REVIEW ARTICLE

# A NARRATIVE REVIEW ON MICROENCAPSULATION: TECHNIQUES AND CLINICAL ASPECTS

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## *ABSTRACT*

*Microencapsulation technique is a process of converting solid, liquid and gases into microcapsules by using various processing techniques. It is used in pharmaceutical, food and agriculture industries. Microencapsulation technique shows broad potential opportunities for resolving important clinical problems by various drug targeting strategies; therefore, aim of current review is to summarize all published studies pertaining to different types of drug delivery system based on microencapsulation. This is a narrative review conducted from the literature from 2009 to 2024. More than 40 articles were downloaded. After abstracting related data, checking quality of data, it is presented in form of PRISMA flow diagram. Most practical microencapsulation techniques and their outcomes; solvent-evaporation method for immiscible phases, fluid-bed/air-suspension coating for taste-masking and linear release of modified-release drugs, phase-separation/coacervation method for desired particle-size for encapsulation, polymeric method, spraying-drying for appropriate particle-size, hot-melt method for taste-masking and maintaining structure of crystals. Clinical benefits accomplished by this technique are; ibuprofen and clarithromycin by taste-masking, fenretinide by enhancing solubility, diclofenac sodium by reducing side-effects, retinol by reduction of toxicity, omeprazole by oral route stability.*

*Drug development by microencapsulation technique is having wide ranging beneficial clinical implications in terms of superiority for uniformity, bioavailability, toxicity, stability and patient acceptance.*

***Keywords:*** *Microencapsulation; pharmaceutical; taste masking; fluid-bed coating; coacervation; spray drying; hot melt*

## INTRODUCTION

Microencapsulation is a process by which tiny particles or droplets surrounded by thin coating and converted into microcapsules.[1] In this technique active ingredient is enclosed in a protective layer.[2] The ingredients (polymers) used for microencapsulation of different products are biocompatible and biodegradable.[3] Such characteristics of natural and synthetic polymers avoid the chances of any toxicity in the body.[4] It provides protection from the environmental factors by encapsulating reactive, sensitive and volatile substances[5] thus microencapsulation improves stability of encapsulated material. Microencapsulation have point of focus from pharmaceutical, nutraceutical, cosmetic and food industry due its ability for protection from degradation, interaction with biological environment and improve absorption.[6] Microencapsulation can be used to modify release of drug substance from pharmaceutical dosage form.[7] Targeted and controlled release drug delivery minimize the unwanted effects.[8] Most crucial phase of microencapsulation is selection of a core material. The selection of material is a determination factor in encapsulation and stability of the targeted product. As a core wall materials; carbohydrates, protein and lipids are generally used alone or in combination to form cover around core material.[9] Additionally with above material

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ethyl cellulose, melamine resin shell, epoxy resins are also used for sustained release behavior.[6]

Oral route of drug administration is most acceptable due to its non-invasiveness and convenience. Taste of the drug substance taken orally is the key factor for evaluation of organoleptic quality of drug dosage form.[10] Unpleasant taste adversely affects patient's adherence to treatment.[11] Various techniques for taste masking have been developed including; addition of sweetener and flavors; however, microencapsulation mask the undesirable taste of different pharmaceutical and nutraceutical products by encapsulating the drug substance and convert it into tasteless product.[12] Microencapsulation is also intended for sustained release drug delivery. Various types of natural and synthetic polymers are used for sustained release activity; which includes a biocompatible and biodegradable polymer such as Poly (lactide-co-glycolide).[4] Sustained release micro pellets not only reduce the frequency of drug administration and adverse effect but also maintain a steady drug plasma concentration.[4]

Stability of a drug product is a critical aspect for development of pharmaceutical dosage form; it ensures efficacy and safety of medication. Maintenance of drug stability under storage condition and human body is a challenge for formulation scientist. Chemical degradation of acid labile products like proton pump inhibitors takes place when taken orally.[13] The degradation produces toxic by-products and also reduce therapeutic efficacy.[14] The stability issue of acid labile products can be overcome by gastric-resistance microencapsulation.[14]

**Importance of microencapsulation:**

i) Protection from deteriorating effects of environmental factors.[15]

ii) Evaporation protection of volatile components.[16]

iii) Masking of undesirable odor and taste of products.[10,12]

iv) Achieving the desired rate for release of drug substance at targeted site.[4]

v) Improving drug stability and protection from degradation due to acidic pH of human stomach.[13]

**Microencapsulation techniques:** There are various microencapsulation techniques available:-

i. Solvent evaporation method.[17] Selection of this procedure depends on the properties of material to be encapsulated. Such as water soluble products; the most suitable procedure is double emulsion type, in which liquid phase containing substance entrapped into water insoluble matrix. Formation of emulsion occurs when aqueous solution containing soluble compound dispersed in dissolved polymer containing organic solvent. This emulsion then dispersed into another secondary aqueous solution; commonly known as W/O/W double emulsion. Due to this process aqueous solution entrapped into polymer and polymer appears as spherical due to secondary emulsion. Produced microspheres are stabilized by surfactant and hardened by continuous stirring to evaporate organic solvent.[17]

ii. Fluid bed coating /Air suspension coating. Fluidized bed coating techniques is used to apply a thin layer coating on surface of granules, pellets, crystal or powder to encapsulate it.[18] Encapsulated material can be taste masked and modify its release. This modification target is achieved through formulation of coating material. In this microencapsulation process three types of coating processes can be applied. These include fluidized bed top spray coating, fluidized bed bottom spray coating and fluidized bed tangential spray coating.[19]

iii. Phase separation/Coacervation method.[20] This process involves the separation of a liquid phase of coating material from a polymeric phase; wrapping in the form of uniform layer around the suspended particles.[20]

iv. Spray drying.[21] A microencapsulation process used for encapsulation of volatile compounds such as essential oils, flavors. Spray drying involved atomization of emulsion in moderate temperature drying area; where immediate evaporation of solvent occur living the essential oils entrapped in microcapsule.[21]

v. Hot-melt.[22] Microencapsulation by hot-melt involves the process of introducing mixture of active ingredient and thermoplastic polymers. Plasticizers are used along with active and thermoplastic polymers to reduce glass transition temperature.[22]

**Clinical Application of Microencapsulated pharmaceutical products:**

Microencapsulation has significantly improved pharmacokinetic properties of drugs. In certain drugs it is observed from literature that by this technique scientists improved pharmacokinetic behavior of drug and decreased minimum effective concentration.[23] It

also resolved many issues related to dosage which we are currently facing.[24] Now extensive research has been started on pharmaceutical products for improving patient compliance and pharmacokinetic properties of drugs. Here are some drugs reported in literature on which successful trials have been conducted.

i. Ibuprofen the most commonly used analgesic have been microencapsulated to resolve the issue of its intake and dosage through oral route.[24]

ii. Microencapsulated adipose tissues derived from mesenchymal cells have been successfully used for treatment of osteoarthritis, without immunosuppressant drugs.[25]

iii. Fenretinide have been evaluated for increasing its solubility for oral cancer chemo-preventive application for future.[26]

iv. To improve stability and achieve maximum antioxidant effect of Moringa oleifera L extract, successful microencapsulation has been achieved. Microencapsulation protected the leaf extract from environmental factors.[27]

v. Thymoquinone is the active ingredient present in black seed oil and have many therapeutic effects. To mask the bitter and unpleasant taste of thymoquinone microencapsulation of black seed oil has been achieved successfully.[28]

vi. Microencapsulation of diclofenac sodium have been performed. It is important for prevention of ulceration associated with its administration.[29]

vii. Modified release pellets of omeprazole for oral liquid dosage form is another milestone for patient with swallowing impairment. This microencapsulated product resist against gastric degradation and released in intestine. These liquid products remain intact for 10 days after reconstitution.[30]

**Current and future trends in microencapsulation:**

Microencapsulation formulated products have many advantages over normally formulated products. Used materials for microencapsulation are biocompatible and biodegradable.[31] Microencapsulation could bring improvement in pharmaceutical current approaches for various disease treatments. It is hope in near future, numerous studies of microencapsulation techniques are believed to result in the development of new and effective clinical protocols.[32]

The main aim of current review is to summarize all published studies pertaining to different types of drug delivery system based on microencapsulation. Microencapsulation technique shows broad potential opportunities for resolving important clinical problems by various drug targeting strategies.[33]

## MATERIALS AND METHODS

In order to write current narrative review on microencapsulation, an orderly literature survey has been conducted from 2009 to 2023 by two authors. To collect the relevant data, title and key word technique were used for collection of appropriate literature.

**Literature Search Strategy:** Data have been collected from Research gate, science direct, springer links, IOP Science, International Journal of Pharmaceutical and Biomedical Science, Journal of Pharmaceutical Science and Research, Polish Pharmaceutical Society and Google scholar. Key words and truncation technique was used for the collection of relevant literature. Fifty articles were downloaded on microencapsulation. The articles selected after abstracting were forty having relevant information, quality and data; further synthesize and presented by PRISMA diagram (Fig. 1).[34] Initial screening was done by two authors and final eligibility was also checked by two authors after reading details of full text of selected literature. Technicalities of article were checked by one author and final check of all data was done by one author. The PRISMA diagram details how studies were identified, the results of abstract screening, the results of full text eligibility assessment; a breakdown of reasons for exclusion, and details of included studies. Full-text eligible articles were forty. All the articles were evaluated for their quality; type of journal, data collection methods, statistical tests, significance values, and interpretations made.

**Quality of Literature Evaluation:**

GRADE (Grading of Recommendation Assessment, Development and Evaluation) criteria were employed for establishing the quality of literature.[35] GRADE is an explicit and transparent system for decision-making regarding the best available literature. The quality of literature by GRADE criteria can be determined by the risk of bias, imprecision, inconsistency, indirectness, publication bias and large magnitude of effect, dose response gradients, and residual confounding in the published and non-published literature.[36]

**Evidence/Literature Inclusion Criteria:** Evidences about types of microencapsulation and clinical application in Literature published from 2009 to 2023.

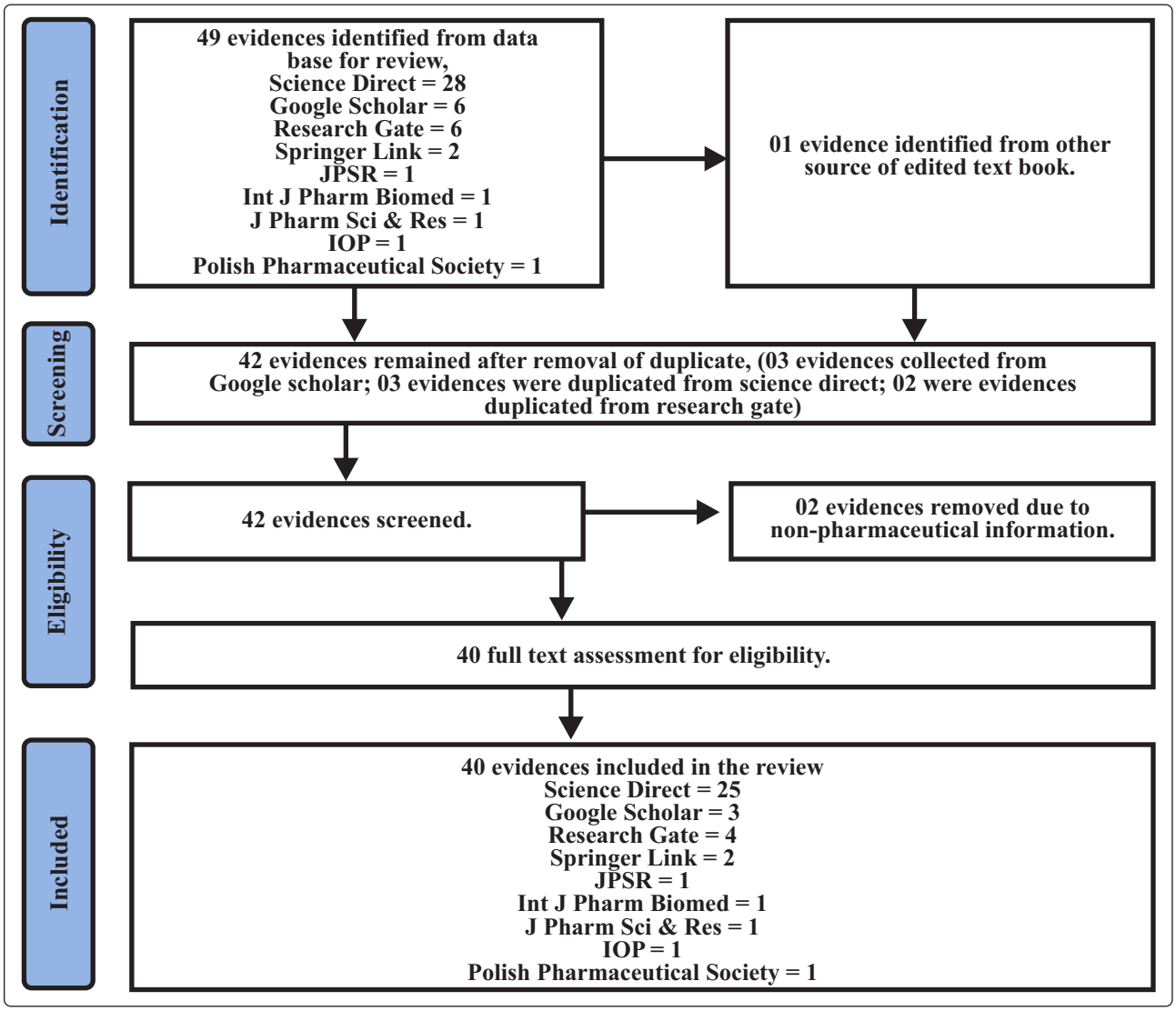


**Figure 1: PRISMA**

**Evidence/Literature Exclusion Criteria:** Literature reported with the microencapsulation techniques having data related to fertilizers and duplicates were excluded.

## RESULTS

Review and literature assessment revealed most practical microencapsulation techniques and their outcomes. (Table I)

The clinical and pharmaceutical benefits e.g. pharmacokinetics, patient compliance and product stability have been achieved by using different microencapsulation techniques. (Table II)

## DISCUSSION

Oxygen supply is essential for metabolic functions of living cells.[37] Oxygen supply through chemical means e.g. by hydrogen per oxide ($H_2O_2$) or naturally are key factors for the growth inhibitions of many anaerobic micro-organisms and thus wound healing.[37] Microencapsulation of gases is a challenging task for formulator but the solvent evaporation technique using poly (methyl methacrylate) solved that issue and successful, stable product can be achieved.[37] Similarly, microencapsulation technique of fluid bed coating have resolved many challenges encountering during the development of effective pharmaceutical formulations.[38] Drug solubility is a major challenge for the development of effective product; especially for the drugs having low intrinsic solubility in gastro-intestinal fluid and belongs to BCS (Biopharmaceutical Classification System) class II drugs.[39,40] By the selection of specific excipients; scientists not only enhanced the solubility and bioavailability, but also modify the target site and protection from first pass effect.[41] It is also evaluated that different approaches can be used for increasing gastrointestinal residence time by magnetic system, high

**Table I: Microencapsulation techniques and outcomes**

| Type of microencapsulation | Study years | First author name | Study design | Outcomes | Quality of Evidence [35] |
|---|---|---|---|---|---|
| Hot-melt extrusion method | 2024 | Nnamdi Ikemefuna Okafor | Clinical study | Improve the palatability and taste masking of pediatric oral formulations.[36] | Moderate |
| Solvent evaporation method | 2014 | Rejendar R. Mallepally | Experimental study | Microencapsulation of miscible and immiscible phases.[37] | High |
| Fluid bed coating/ Air suspension coating | 2017; 2019 | J. Mandic; Mohammad Foroughi-Dahr; Samar Elasmaligy | Experimental studies | Taste masking and linear release for modified release products.[38, 39] | High; Moderate |
| Phase separation / Coacervation method | 2022 | Ruifeng Wang | Experimental study | Paddle stirring can be customized to produce desired particle size of encapsulated material.[20] | Moderate |
| Spray drying | 2020 | Jiayue Guo | Experimental study | Manufacturing of finer, spherical and regular particle.[21] | Low |
| Hot melt | 2015 | Manjeet B. Pimparade | In-vitro, In-vivo experimental study | Effective taste masking, and maintaining structure crystallinity of API (Active Pharmaceutical Ingredient).[40] | High |

density system, muco-adhesive system, swelling and expanding system as well as floating system.[42] Floating system can easily have achieved by applying multi-layer coating as a source of $CO_2$ along with extended time for drug release.[42] Processing parameters like, inlet air, inlet temperature, fluidization, spray rate, spray speed, dispersion contents and viscosity plays the vital role to achieve product yield, content uniformity and product performance.[42] Drug protection from the low pH and enzyme of stomach is also a challenge for formulators.[42] Application of specific excipients by microencapsulation drug substances have been protected from degradation by GIT environmental factors and enhances the product stability.[43] Repeated dosage intake is a challenge to manage patient compliance and adherence to treatment course. To avoid that noncompliance high potency with extended release period is required. Microencapsulation with fluid bed coating technique has resolved this issue. To achieve that goal; different formulation using various polymers have been designed. Currently one of these formulations is discussed in this review included diclofenac sodium sustain release pellets.[38,43]

Pediatric dosage acceptance is also a challenge; many drugs with bitter taste are used for treatment. Due to bitter taste, it is not possible to give medication in as such form to children. Different dosage forms like tablets and capsules are also not acceptable by children. Fluid bed coating by microencapsulation technique for taste masking of bitter drugs like clarithromycin have been achieved.[43] Similarly, safe delivery of probiotic to support antibiotic for treatment of bacterial infection is another challenge for formulator. One of the problem associated with their transfer to site of action is the gastric path and their time dependent release. These problem have been resolved by spray drying technique. After spray drying, probiotic is converted into erodible tablets using beeswax and carboxymethylcellulose sodium.[44] These excipients not only delayed the probiotic release but also prevent from acidic environment of gastrointestinal tract, ensure intestinal colonization and vaginal mucosa for support of effective treatment.[44]

Retinol is an important retinoid for the treatment of acne, wrinkle, aging induced by UV (Ultraviolet) light and for treatment of chronic skin condition like psoriasis and ichthyosis.[45] That compound is degraded when exposed to light and oxygen; in as such form it is very difficult to incorporate in dosage form. So, to protect this compound from environmental factors to enhance its stability; microencapsulation technique was applied; the technique not only improve its stability but also reduced

**Table II: Clinical and pharmaceutical benefits of microencapsulation techniques**

| Microencapsulated Product | Study years | First author name | Study design | Outcomes | Quality of Evidence [35] |
|---|---|---|---|---|---|
| *Lactobacillus* and *Bifidobacterium* as probiotics | 2024 | M. Lavanya | Experimental animal study | Polymeric or lipid-based nanoparticles improved the bioavailability of probiotics and inhibited the neuro-degeneration which caused by Alzheimer's disease.[41] | High |
| Ibuprofen | 2013 | N. Carreras | Experimental study (Solvent evaporation method) | Taste masking.[42] | Moderate |
| Adipose tissue | 2018 | Seongjae Choi | Animal study | Treatment of osteoarthritis.[43] | Moderate |
| Fenretinide | 2020 | Kari Nieto | In-vitro, In-vivo experimental study | Drug solubility enhancement.[26] | High |
| Bifidobacterium breve BC204 | 2018 | Barbara Giordani | In-vitro, Ex-vivo experimental study | Protection from gastrointestinal and urogenital infections.[44] | Low |
| Moringa olifera leaf extract | 2023 | Jaine Mailho Gimenis | In-vitro, In-vivo experimental study | Product stability.[27] | Low |
| Thymoquinone | 2020 | Hamzeh Alkhatib | Full factorial ($3^2$) design study | Taste masking.[45] | High |
| Diclofenac sodium | 2022 | Nesrin F. Taha | In-vitro, In-vivo experimental study | Reduction in side effects.[46] | High |
| $Reti_{nol}$ | 2018 | C. Wyatt Shields IV | Double blind human study | Product safety and reduction of toxic effects.[47] | Moderate |
| Omeprazol | 2019 | Federica Ronchi | Experimental study | Oral route stability of API (Active Pharmaceutical Ingredient).[30] | Moderate |
| Clarithromycin | 2012 | Harshada Sanjay Akre | Experimental study | Taste masking.[48] | High |

the toxic effect e.g. skin irritation. The suitable excipient for microencapsulation is selected i.e. silicone due to biocompatibility and stability. The encapsulation of retinol is done by using phase separation technique.[45]

The most common form of arthritis is the osteoarthritis, which is degenerative disease of joints.[45] It commonly affects quality of life by causing pain, stiffness and disability. Various types of techniques have been applied for the treatment of this condition for the regeneration of joints. Among different techniques, adipose tissue derived mesenchymal stem cell have better control over other methods.[46] The technique improved quality of life in human after intra-articular injection of adipose tissue mesenchymal stem cells by reducing pain, knee joint cartilage defects and improving functionality.[47] These adipose tissue mesenchymal stem cells are alginate base microencapsulated.[47] These microencapsulated adipose tissue mesenchymal cells act as mechanical barrier, extracellular material and improves cell viability; which also allow release of stem cell produced growth factors and substances that act as anti-inflammatory for surrounding effected area.[48]

The plant oriented herb from Moringa oleifera L. has many health benefits. It is an important antioxidant and provide protection against various conditions by having characteristics of hypoglycemia, antimicrobial, anti-inflammatory, antispasmodic, antiasthmatic and hypocholesterolemic.[49] Skin is the largest organ of the body and provides protection against foreign invaders. Due to antioxidant activity of moringa leaf extract it provides protection to skin from stress oxidation, which leads to wrinkles and aging.[49] To obtain maximum

pharmacological effect for body, it is very important to obtain stable formulation. For this purpose, it is now possible to obtain moringa leaf extract liposomes by microencapsulation technique.[49]

## CONCLUSION

Drug development by microencapsulation technique is having wide ranging beneficial clinical implications. Microencapsulated products have superiority compared to other product in reference to their uniformity, bioavailability, toxicity, stability and patient acceptance.

### Limitations and recommendations:

There are many issues related to the advancement of microencapsulation techniques. Despite advancements, selection of core material, material required for coating e.g. cheaper biopolymer and processing are still challenges for pharmaceutical scientists. More studies on bioassays are required for encapsulation of food anti-oxidants. Due to high cost of manufacturing of microencapsulated products; few pharmaceutical industries are having interest in this technique. In Pakistan, the only techniques applied for microencapsulation is fluid bed coating. Organ specific drug delivery is another challenge for this product. The advancement in this area is possible with research institute and technology transfer, which should be supported at national level.

**Authors' contributions:**

Sheikh Abdul Khaliq: Critical Review, Facilitated for Reagents / Material Analysis

Sarfraz Ahmad: Experimentation/ Study Conduction, Manuscript Writing

Kamran Haidar: Conception of study/ Designing/ Planning, Experimentation / Study Conduction

Muhammad Jiyad Shaikh: Experimentation/ Study Conduction, Analysis/ Interpretation/ Discussion

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