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### **Electro-hydrodynamic assisted synthesis of lecithin-stabilized peppermint oil-loaded alginate microbeads for intestinal drug delivery**

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#### **Abstract**

Peppermint oil (PO) is the most prominent oil used in pharmaceutical formulations with its significant therapeutic value. In this sense, this oil is attracting considerable attention from the scientific community due to its traditional therapeutic claim, biological and pharmacological potential in recent research. An organic solvent-free and environment-friendly electrohydrodynamic assisted (EHDA) technique was employed to prepare PO-loaded alginate microbeads. The current study deals with the development, optimization, in vitro characterization, in vivo gastrointestinal tract drug distribution and ex-vivo mucoadhesive properties, antioxidant, and anti-inflammatory effects of PO-loaded alginate microbeads. The optimization results indicated the voltage and flow rate have a significant influence on microbeads size and sphericity factor and encapsulation efficiency. All these optimized microbeads showed a better drug release profile in simulated intestinal fluid (pH 6.8) at 2 h. However, a minor release was found in acidic media (pH 1.2) at 2 h. The optimized formulation showed excellent mucoadhesive properties in ex-vivo and good swelling characterization in intestine media. The microbeads were found to be well distributed in various parts of the intestine in in vivo study. PO-loaded alginate microbeads similarly showed potential antioxidant effects with drug release. The formulation exhibited possible improvement of irritable bowel syndrome (IBS) in MO-induced rats. It significantly suppressed proinflammatory cytokines, i.e., interleukin- IL-1 $\beta$ , and upregulated anti-inflammatory cytokine expression, i.e., IL-10. It would be a promising approach for targeted drug release after oral administration and could be considered an anti-inflammatory therapeutic strategy for treating IBS. © 2021 Elsevier B.V.

#### **Author Keywords**

Electrohydrodynamic; Emulsion; GIT distribution; Microencapsulation; Peppermint oil

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#### **References**

- Hosseini, S.M., Hosseini, H., Mohammadifar, M.A., Mortazavian, A.M., Mohammadi, A., Khosravi-Darani, K., Shojaee-Aliabadi, S., Khaksar, R.

### **Incorporation of essential oil in alginate microparticles by multiple emulsion/ionic gelation process**

(2013) *Int. J. Biol. Macromol.*, 62, pp. 582-588.

- Deka, C., Deka, D., Bora, M.M., Jha, D.K., Kakati, D.K.

### **Synthesis of peppermint oil-loaded chitosan/alginate polyelectrolyte complexes and study of their antibacterial activity**

(2016) *J. Drug Deliv. Sci. Technol.*, 35, pp. 314-322.

- Banerjee, S., Chattopadhyay, P., Ghosh, A., Goyary, D., Karmakar, S., Veer, V.  
**Influence of process variables on essential oil microcapsule properties by carbohydrate polymer-protein blends**  
(2013) *Carbohydr. Polym.*, 93, pp. 691-697.
- Dima, C., Cotârlet, M., Alexe, P., Dima, S.  
**Microencapsulation of essential oil of pimento [Pimenta dioica (L) Merr.] by chitosan/k-carrageenan complex coacervation method**  
(2014) *Innov. Food Sci. Emerg. Technol.*, 22, pp. 203-211.
- Chan, L.W., Lim, L.T., Heng, P.W.S.  
**Microencapsulation of oils using sodium alginate**  
(2000) *J. Microencapsul.*, 17, pp. 757-766.
- Nikoo, A.M., Kadkhodaee, R., Ghorani, B., Razzaq, H., Tucker, N.  
**Electrospray-assisted encapsulation of caffeine in alginate microhydrogels**  
(2018) *Int. J. Biol. Macromol.*, 116, pp. 208-216.
- De Barros Fernandes, R.V., Borges, S.V., Botrel, D.A.  
**Gum arabic/starch/maltodextrin/inulin as wall materials on the microencapsulation of rosemary essential oil**  
(2014) *Carbohydr. Polym.*, 101, pp. 524-532.
- El Asbahani, A., Miladi, K., Badri, W., Sala, M., Addi, E.A., Casabianca, H., Elaissari, A.  
**Essential oils: from extraction to encapsulation**  
(2015) *Int. J. Pharm.*, 483, pp. 220-243.
- Paques, J.P., Sagis, L.M.C., van Rijn, C.J.M., van der Linden, E.  
**Nanospheres of alginate prepared through w/o emulsification and internal gelation with nanoparticles of CaCO<sub>3</sub>**  
(2014) *Food Hydrocoll.*, 40, pp. 182-188.
- Pawar, S.N., Edgar, K.J.  
**Alginate derivatization: a review of chemistry, properties and applications**  
(2012) *Biomater.*, 33, pp. 3279-3305.
- Rees, D.  
**Structure, conformation, and mechanism in the formation of polysaccharide gels and networks**  
(1969) *Adv. Carbohydr. Chem. Biochem.*, 24, pp. 267-332.
- Chan, E.-S.  
**Preparation of ca-alginate beads containing high oil content: influence of process variables on encapsulation efficiency and bead properties**  
(2011) *Carbohydr. Polym.*, 84, pp. 1267-1275.
- Doolaanea, A.A., Mansor, N.I., Mohd Nor, N.H., Mohamed, F.  
**Co-encapsulation of Nigella sativa oil and plasmid DNA for enhanced gene therapy of Alzheimer's disease**  
(2016) *J. Microencapsul.*, 33, pp. 114-126.
- Hua, S.  
**Advances in Oral drug delivery for regional targeting in the gastrointestinal tract-influence of physiological, pathophysiological and pharmaceutical factors**  
(2020) *Front. Pharmacol.*, 11, p. 524.

- Niranjana Prabhu, T., Prashantha, K.  
**A review on present status and future challenges of starch-based polymer films and their composites in food packaging applications**  
(2018) *Polym. Compos.*, 39, pp. 2499-2522.
- Ansary, R.H., Rahman, M.M., Awang, M.B., Katas, H., Hadi, H., Doolaanea, A.A.  
**Preparation, characterization, and in vitro release studies of insulin-loaded double-walled poly (lactide-co-glycolide) microspheres**  
(2016) *Drug Deliv. Transl. Res.*, 6, pp. 308-318.
- Nayak, A.K., Das, B., Maji, R.  
**Calcium alginate/gum arabic microbeads containing glibenclamide: development and in vitro characterization**  
(2012) *Int. J. Biol. Macromol.*, 51, pp. 1070-1078.
- Azad, A.K., Al-Mahmood, S.M.A., Chatterjee, B., Wan Sulaiman, W.M.A., Elsayed, T.M., Doolaanea, A.A.  
**Encapsulation of black seed oil in alginate beads as a pH-sensitive carrier for intestine-targeted drug delivery: in vitro, in vivo and ex vivo study**  
(2020) *Pharmaceutics*, 12, p. 219.
- Alkhatib, H., Mohamed, F., Akkawi, M.E., Alfatama, M., Chatterjee, B., Doolaanea, A.A.  
**Microencapsulation of black seed oil in alginate beads for stability and taste masking**  
(2020) *J. Drug Deliv. Sci. Technol.*, 60.
- Bera, H., Gaini, C., Kumar, S., Sarkar, S., Boddupalli, S., Ippagunta, S.R.  
**HPMC-based gastroretentive dual working matrices coated with Ca 2 ion crosslinked alginate -fenugreek gum gel membrane**  
(2016) *Mater. Sci. Eng. C*, 67, pp. 170-181.
- Schmidt, E., Bail, S., Buchbauer, G., Stoilova, I., Atanasova, T., Stoyanova, A., Jirovetz, L.  
**hChemical composition, olfactory evaluation and antioxidant effects of essential oil from Mentha x piperita**  
(2009) *Nat. Prod. Commun.*, 4.  
1934578X0900400819
- Bera, H., Ang, S.R., Chiong, S.W., Chan, C.H., Abbasi, Y.F., Law, L.P.  
**& Venugopal, V., Core-shell structured pullulan-based nanocomposites as erlotinib delivery shuttles**  
(2019) *Int. J. Polym. Mater.*, pp. 1-12.
- Bera, H., Abbasi, Y.F., Yoke, F.F., Seng, P.M., Kakoti, B.B., Ahmmmed, S.M., Bhatnagar, P.  
**Ziprasidone-loaded arabic gum modified montmorillonite-tailor-made pectin based gastroretentive composites**  
(2019) *Int. J. Biol. Macromol.*, 129, pp. 552-563.
- Bera, H., Abbasi, Y.F., Gajbhiye, V., Liew, K.F., Kumar, P., Tambe, P., Yang, M.  
**Carboxymethyl fenugreek galactomannan-g-poly (N-isopropylacrylamide-co-N, N'-methylene-bis-acrylamide)-clay based pH/temperature-responsive nanocomposites as drug-carriers**  
(2020) *Mater. Sci. Eng. C*,

- Bera, H., Mothe, S., Maiti, S., Vanga, S.  
**Carboxymethyl fenugreek galactomannan-gellan gum-calcium silicate composite microbeads for glimepiride delivery**  
(2018) *Int. J. Biol. Macromol.*, 107, pp. 604-614.
- Bera, H., Kandukuri, S.G., Nayak, A.K., Boddupalli, S.  
**Alginate –sterculia gum gel-coated oil-entrapped alginate beads for gastroretentive risperidone delivery**  
(2015) *Carbohydr. Polym.*, 120, pp. 74-84.
- Rahaiee, S., Hashemi, M., Shojaosadati, S.A., Moini, S., Razavi, S.H.  
**Nanoparticles based on crocin loaded chitosan-alginate biopolymers: antioxidant activities, bioavailability and anticancer properties**  
(2017) *Int. J. Biol. Macromol.*, 99, pp. 401-408.
- Bera, H., Ippagunta, S.R., Kumar, S., Vangala, P.  
**Core-shell alginate-ghatti gum modified montmorillonite composite matrices for stomach-specific flurbiprofen delivery**  
(2017) *Mater. Sci. Eng. C*, 76, pp. 715-726.
- Dhaliwal, S., Jain, S., Singh, H.P., Tiwary, A.K.  
**Mucoadhesive microspheres for gastroretentive delivery of acyclovir: in vitro and in vivo evaluation**  
(2008) *AAPS J.*, 10, p. 322.
- Kimball, E.S., Palmer, J.M., D'Andrea, M.R., Hornby, P.J., Wade, P.R.  
**Acute colitis induction by oil of mustard results in later development of an IBS-like accelerated upper GI transit in mice**  
(2005) *Am. J. Phys. Gastrointest. Liver*, 288, pp. G1266-G1273.
- Shao, P., Ma, H., Zhu, J., Qiu, Q.  
**Impact of ionic strength on physicochemical stability of o/w emulsions stabilized by Ulva fasciata polysaccharide**  
(2017) *Food Hydrocoll.*, 69, pp. 202-209.
- Sui, X., Bi, S., Qi, B., Wang, Z., Zhang, M., Li, Y., Jiang, L.  
**Impact of ultrasonic treatment on an emulsion system stabilized with soybean protein isolate and lecithin: its emulsifying property and emulsion stability**  
(2017) *Food Hydrocoll.*, 63, pp. 727-734.
- Benavides, S., Cortés, P., Parada, J., Franco, W.  
**Development of alginate microspheres containing thyme essential oil using ionic gelation**  
(2016) *Food Chem.*, 204, pp. 77-83.
- Banerjee, S., Chattopadhyay, P., Ghosh, A., Goyary, D., Karmakar, S., Veer, V.  
**Influence of process variables on essential oil microcapsule properties by carbohydrate polymer–protein blends**  
(2013) *Carbohydr. Polym.*, 93, pp. 691-697.
- **USP 42/NF 37**  
(2019), United States Pharmacopoeia Convention Inc. Rockville, MD, USA

- Yilmaztekin, M., Levic, S., Kaluševic, A., Cam, M., Bugarski, B., Rakic, V., Nedovic, V.  
**Characterisation of peppermint (*Mentha piperita L.*) essential oil encapsulates**  
(2019) *J. Microencapsul.*, 36, pp. 109-119.
- Chen, H., Zhong, Q.  
**A novel method of preparing stable zein nanoparticle dispersions for encapsulation of peppermint oil**  
(2015) *Food Hydrocoll.*, 43, pp. 593-602.
- Hadiseh, Q., Alemzadeh, I.  
**Encapsulation of peppermint oil with arabic gum-gelatin by complex coacervation method**  
(2013) *Int. J. Eng.*, 26, pp. 807-814.
- Baimark, Y., Srisuwan, Y.  
**Preparation of alginate microspheres by water-in-oil emulsion method for drug delivery: effect of Ca<sup>2+</sup> post-crosslinking**  
(2014) *Adv. Powder Technol.*, 25, pp. 1541-1546.
- Koo, S.Y., Cha, K.H., Song, D.-G., Chung, D., Pan, C.-H.  
**Microencapsulation of peppermint oil in an alginate –pectin matrix using a coaxial electrospray system**  
(2014) *Int. J. Food Sci. Technol.*, 49, pp. 733-739.
- Yilmaztekin, M., Lević, S., Kalušević, A., Cam, M., Bugarski, B., Rakić, V., Pavlović, V., Nedović, V.  
**Characterisation of peppermint (*Mentha piperita L.*) essential oil encapsulates**  
(2019) *J. Microencapsul.*, 36 (2), pp. 109-119.
- Prakash, N., Yunus, M.  
**Fourier transform infrared spectroscopy analysis of oil of *Mentha arvensis* grown at sites varying with vehicular traffic loads in Lucknow city, India**  
(2013) *Int. J. Environ.*, 2, pp. 16-25.
- Shetta, A., Kegere, J., Mamdouh, W.  
**Comparative study of encapsulated peppermint and green tea essential oils in chitosan nanoparticles: encapsulation, thermal stability, in-vitro release, antioxidant and antibacterial activities**  
(2019) *Int. J. Biol. Macromol.*, 126, pp. 731-742.
- Lim, L.Y., Wan, L.S.  
**Propranolol hydrochloride binding in calcium alginate beads**  
(1997) *Drug Dev. Ind. Pharm.*, 23, pp. 973-980.
- Mukhopadhyay, P., Sarkar, K., Soam, S., Kundu, P.P.  
**Formulation of pH-responsive carboxymethyl chitosan and alginate beads for the oral delivery of insulin**  
(2013) *J. Appl. Polym. Sci.*, 129, pp. 835-845.
- Chuang, J.J., Huang, Y.Y., Lo, S.H., Hsu, T.F., Huang, W.Y., Huang, S.L., Lin, Y.S.  
**Effects of pH on the shape of alginate particles and its release behavior**  
(2017) *Int. J. Polym. Sci.*,

- Malakar, J., Datta, P.K., Purakayastha, S.D., Dey, S., Nayak, A.K.  
**Floating capsules containing alginate -based beads of salbutamol sulfate: in vitro-in vivo evaluations**  
(2014) *Int. Biol. Macromol.*, 64, pp. 181-189.
- Nayak, A.K., Pal, D., Santra, K.  
**Swelling and drug release behavior of metformin HCl-loaded tamarind seed polysaccharide-alginate beads**  
(2016) *Int. J. Biol. Macromol.*, 82, pp. 1023-1027.
- Pasparakis, G., Bouropoulos, N.  
**Swelling studies and in vitro release of verapamil from calcium alginate and calcium alginate -chitosan microbeads**  
(2006) *Int. J. Pharm.*, 323, pp. 34-42.
- Bajpai, S.K., Sharma, S.  
**Investigation of swelling/degradation behaviour of alginate microbeads crosslinked with Ca<sup>2+</sup> and Ba<sup>2+</sup> ions**  
(2004) *React. Funct. Polym.*, 59, pp. 129-140.
- Chen, Y.C., Ho, H.O., Liu, D.Z., Siow, W.S., Sheu, M.T.  
**Swelling/floating capability and drug release characterizations of gastroretentive drug delivery system based on a combination of hydroxyethyl cellulose and sodium carboxymethyl cellulose**  
(2015) *PLoS One*, 10.
- Deng, K.L., Dong, L.R., Shi, Y.E., Gou, Y.B., Li, Q., Wang, S.L.  
**Drug release behaviors of a pH/temperature sensitive hydrogel bead with core-shelled structure**  
(2011) *Adv. Mater. Res.*, 148-149, pp. 1427-1430.
- Pongjanyakul, T., Puttipipatkhachorn, S.  
**Modulating drug release and matrix erosion of alginate matrix capsules by microenvironmental interaction with calcium ion**  
(2007) *Eur. J. Pharm. Biopharm.*, 67, pp. 187-195.
- Lucinda-Silva, R.M., Salgado, H.R.N., C, R.  
**Alginate-chitosan systems: in vitro controlled release of triamcinolone and in vivo gastrointestinal transit**  
(2010) *Carbohydr. Polym.*, 81, pp. 260-268.
- Lee, H.Y., Chan, L.W., Heng, P.W.S.  
**Influence of partially cross-linked alginate used in the production of alginate microspheres by emulsification**  
(2005) *J. Microencapsul.*, 22, pp. 275-280.
- Berkland, C., Kipper, M.J., Narasimhan, B., Kim, K.K., Pack, D.W.  
**Microsphere size, precipitation kinetics and drug distribution control drug release from biodegradable polyanhydride microspheres**  
(2004) *J. Control. Release*, 94, pp. 129-141.
- Wang, H., Gong, X., Guo, X., Liu, C., Fan, Y.Y., Zhang, J., Li, W.  
**Characterization, release, and antioxidant activity of curcumin-loaded sodium alginate/ZnO hydrogel microbeads**

(2019) *Int. J. Biol. Macromol.*, 121, pp. 1118-1125.

- Lee, J.S., Kim, E.J., Chung, D., Lee, H.G.

**Characteristics and antioxidant activity of catechin-loaded calcium pectinate gel microbeads prepared by internal gelation**

(2009) *Colloids Surf. B: Biointerfaces*, 74, pp. 17-22.

- Agarwal, T., Narayana, S.G.H., Pal, K., Pramanik, K., Giri, S., Banerjee, I.

**Calcium alginate-carboxymethyl cellulose microbeads for colon-targeted drug delivery**

(2015) *Int. J. Biol. Macromol.*, 75, pp. 409-417.

- Bashashati, M., Moossavi, S., Cremon, C., Barbaro, M.R., Moraveji, S., Talmon, G., Lee, O.Y.

**Colonic immune cells in irritable bowel syndrome: a systematic review and meta-analysis**

(2018) *Neurogastroenterol. Motil.*, 30.

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