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Effect of Alginate and Surfactant on Physical Properties of Oil Entrapped Alginate Bead Formulation of Curcumin

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***Abstract*—**Oil entrapped floating alginate beads of curcumin were developed and characterized. Cremophor EL, Cremophor RH and Tween 80 were utilized to improve the solubility of the drug. The oil-loaded floating gel beads prepared by emulsion gelation method contained sodium alginate, mineral oil and surfactant. The drug content and % encapsulation declined as the ratio of surfactant was increased. The release of curcumin from 1% alginate beads was significantly more than for the 2% alginate beads. The drug released from the beads containing 25% of Tween 80 was about 70% while a higher drug release was observed with the beads containing Cremophor EL or Cremohor RH (approximately 90%). The developed floating beads of curcumin powder with surfactant provided a superior drug release than those without surfactant. Floating beads based on oil entrapment containing the drug solubilized in surfactants is a new delivery system to enhance the dissolution of poorly soluble drugs.

***Keywords*—**Alginate, curcumin, floating drug delivery, oil entrapped bead.

I. Introduction

CURCUMIN, is a natural product commonly used as a spice for cooking and is obtained from the rhizomes of the herb *Curcuma longa* (Zingiberaceae family) in which it is the principal curcuminoid. It is an orange-yellow, polyphenolic, crystalline powder that is practically insoluble in water [1]. It has a variety of biological and pharmacological activities including anti-oxidative [2], anti-inflammatory [3], [4], antimicrobial [5], anti-ulcer [6], [7], anti-proliferative [8] and anti-cancer [9]. A large number of reports and numerous reviews have shown that curcumin has been used to treat several diseases and has other favorable biological effects. However, the pharmacological effects of curcumin are limited due to its low aqueous solubility and rapid metabolism in the gastrointestinal tract. There are several strategies to overcome these problems of curcumin including producing nanoparticles, liposomes, micelles, and phospholipid complexes. These systems allow for better absorption, enhanced permeability, and resistance to metabolic processes in the intestine [10]. Another method used to improve the solubility of hydrophobic/lipophilic drugs is to combine it with surfactants. Non ionic surfactants have shown many benefits such as enhanced bioavailability, and lower side effects compared to ionic surfactants. Ratanajiajaroen et al. [11] showed that the incorporation of curcumin together with Tween 20, a non-ionic surfactant, at a concentration of 2% v/v in acetate buffer pH 5.5 increased the solubility of curcumin from 11ng/mL to 0.767mg/mL. In addition there was a higher release rate of curcumin from chitin beads observed as the amount of Tween 20 increased. Song et al. [12] showed that calcium alginate beads containing different amounts of the food emulsifiers (Tween 80 and Span 80) produced nearly a complete release of curcumin in an aqueous buffer solution (pH 7.2) within 20h. With an increase of the Tween-80 concentration that ranged from 1-3% at a fixed Span 80 concentration, the amount of drug release increased by about 7 fold.

Floating drug delivery systems (FDDS) are dosage forms with a less bulk density than normal gastric contents. They could provide a continuous release of the drug while in the stomach without affecting the rate of gastric emptying. FDDS can be classified into 2 formulation approaches including effervescent and non-effervescent systems [13]-[15]. For effervescent systems, the buoyancy can be achieved by the generation of carbon dioxide gas bubbles when the systems contact the gastric fluid. In another approach, the floating can be obtained using swellable polymers or incorporating low density materials into the systems. Uses of various low density oils such as mineral oils, olive oil, sunflower oil, groundnut oil and castor oil have all been reported to assist in producing floating gel beads. The aim of this study was to develop oil entrapped floating alginate beads containing curcumin solubilized by a surfactant. The effect of the alginate concentration and surfactant on the physical properties and the *in vitro* drug release from gel beads were studied.

II. Material and Method

A. Materials

Curcumin was obtained from Sigma Aldrich (Buchs, Switzerland). Sodium alginate (food grade) was from High Science limited partnership (Songkla, Thailand) Cremophor RH40™ (polyoxyethylene castor oil derivatives) and Cremophor EL™ (polyoxyethylene castor oil derivatives) were from BASF (Ludwigshafen, Germany). Tween® 80 (Polysorbate 80) was from PC Drug Center Co., Ltd.

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(Bangkok, Thailand). Mineral oil was from Namsiangcompany limited (Bangkok, Thailand). Methanol (AR grade) and calcium chloride were from RCI Labscan (Bangkok, Thailand). All other chemicals were of analytical grade.

B. Formulation and Preparation of Floating Oil Entrapped Alginate Beads of Curcumin

All formulations of oil entrapped floating alginate beads are presented in Table I. In brief, a solution of sodium alginate was prepared by adding sodium alginate (1% and 2%w/v) in distilled water. Curcumin was mixed with each surfactant then added into the alginate solution and stirred until it became homogeneous. The mineral oil was added and stirred at 1000 rpm continuously to get a stable o/w emulsion. The emulsion was extruded drop wise through a syringe with a 1mm inner diameter into a 0.1 M calcium chloride solution (100ml) with gentle agitation at room temperature. The calcium alginate beads were allowed to cure for 10min. Then, they were separated from the solution by filtration and rinsed with deionized water. Finally, they were dried in an oven (Memmert®, Germany) at 40ºC until a constant weight was obtained. The dried oil-entrapped calcium alginate beads containing curcumin were stored in a desiccator until used.

TABLE I
COMPOSITION AND CHARACTERIZATION OF CURCUMIN OIL-ENTRAPPED ALGINATE BEADS FORMULATIONS

Formulation	Curcumin (%)	Alginate (%)	Mineral oil (%)	Surfactant			Drug content (mg±SD)	%Encapsulation (±SD)	Floating Duration (h)
				Cremophor EL (%)	Cremophor RH (%)	Tween 80 (%)			
control	1	1	10				6.54±0.18	73.69±2.04	>8
1ME5	1	1	10	5			3.15±0.04	44.39±0.61	>8
1ME10	1	1	10	10			2.37±0.02	43.68±0.44	>8
1ME15	1	1	10	15			1.81±0.05	42.55±1.22	>8
1ME20	1	1	10	20			1.76±0.04	41.11±0.94	>8
1ME25	1	1	10	25			1.60±0.01	40.28±0.23	>8
2ME5	1	2	10	5			2.81±0.05	43.94±0.76	>8
2ME10	1	2	10	10			2.30±0.04	41.52±0.72	>8
2ME15	1	2	10	15			1.79±0.06	40.41±1.33	>8
2ME20	1	2	10	20			1.69±0.02	39.76±0.58	>8
2ME25	1	2	10	25			1.48±0.02	38.13±0.49	>8
1MR5	1	1	10		5		3.38±0.02	44.72±0.33	>8
1MR10	1	1	10		10		2.49±0.04	42.73±0.71	>8
1MR15	1	1	10		15		2.05±0.04	42.98±0.83	>8
1MR20	1	1	10		20		2.03±0.03	42.54±0.70	>8
1MR25	1	1	10		25		1.99±0.02	42.14±0.59	>8
2MR5	1	2	10		5		2.89±0.08	45.90±1.33	>8
2MR10	1	2	10		10		2.38±0.02	43.25±0.38	>8
2MR15	1	2	10		15		1.89±0.03	40.47±0.56	>8
2MR20	1	2	10		20		1.73±0.02	39.60±0.53	>8
2MR25	1	2	10		25		1.51±0.02	37.02±0.58	>8
1MT5	1	1	10			5	2.97±0.08	40.49±1.13	>8
1MT10	1	1	10			10	2.50±0.03	39.60±0.45	>8
1MT15	1	1	10			15	2.06±0.02	38.15±0.37	>8
1MT20	1	1	10			20	1.94±0.01	37.86±0.16	>8
1MT25	1	1	10			25	1.87±0.02	36.66±0.47	>8
2MT5	1	2	10			5	3.00±0.08	44.10±1.17	>8
2MT10	1	2	10			10	2.21±0.03	37.87±0.46	>8
2MT15	1	2	10			15	1.94±0.02	37.10±0.36	>8
2MT20	1	2	10			20	1.88±0.01	36.10±0.25	>8
2MT25	1	2	10			25	1.72±0.03	35.70±0.86	>8

C. Drug Content and Drug Entrapment Efficiency

After drying, accurately weighed quantities of approximately 100mg curcumin loaded beads were pulverized and dissolved in 50ml of methanol. Then, the solution was sonicated and filtered. An ultraviolet–visible spectrophotometer (Spectronic Genesys®, USA) was used to evaluate the absorbance values of curcumin at the wavelength of 425nm [17]. The actual amount of curcumin within the bead was determined by backcalculating from the data produced from a predetermined calibration curve of curcumin in methanol. The determinations were made in triplicate. The entrapment efficiency (EE) was calculated based on the ratio of the amount of drug present in the beads to the amount of drug used in the loading process [11], [16], [17].

$$\mathrm{EE}(\%) = \frac{\text{Actual amount aof curcumin within the beads}}{\text{Initial amount of curcumin taken for loading studies}} \text{x} 100 \quad (1)$$

D. Buoyancy Test

One gram of the floating beads was incorporated into the test medium (70ml of 0.1 N HCl) that was agitated by a magnetic stirrer at 75rpm and 37°C. The floating behavior of the beads in the test medium was observed for a period of 8h [18], [19].

E. In vitro Drug Release

In vitro release studies were carried out using the USP XXIII Dissolution Apparatus II (paddle type). The floating beads were dropped into 900ml of HCl buffer pH 1.2 maintained at 37±0.5°C and stirred at a speed of 50rpm [16], [20]. At different time intervals, a 5ml aliquot was withdrawn and the volume was replaced with an equivalent amount of fresh dissolution medium kept at 37°C. The collected samples were filtered and analyzed at 425nm [18] using an ultraviolet–visible spectrophotometer.

III. Results and Discussion

A. Drug Content, Percent Encapsulation and Floating Duration

The drug content and percentage encapsulation of the prepared formulations are given in Table I. 1MR5 revealed the highest drug loading value of 3.38±0.02mg per 100mg whereas 2MR25 demonstrated the least value of 1.51±0.02mg per 100mg of floating gel beads. Both the drug content and the percentage encapsulation were significantly reduced when the quantity of the surfactant was increased from 5 to 25 % w/w. The percentage encapsulation of all formulations was in the range of 35.70±0.86 to 45.90±1.33.

B. The Appearance of the Floating Beads

The floating alginate beads were yellow in color. The surface of the beads was smooth and dry. For the 1% alginate beads, all had an acceptable spherical shape. The beads made from 2% alginate exhibited nearly like droplet shape for the reason that it had a high viscosity. Moreover, the 2% alginate beads with higher Tween 80 presented more droplet shape over the beads made from Cremophor EL and Cremophor RH.

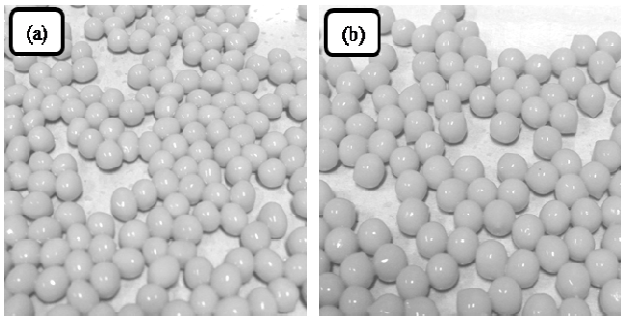


Fig. 1 The appearance of floating alginate beads containing 1% alginate (a) or 2% alginate (b) and 25% CremophoreRH before drying

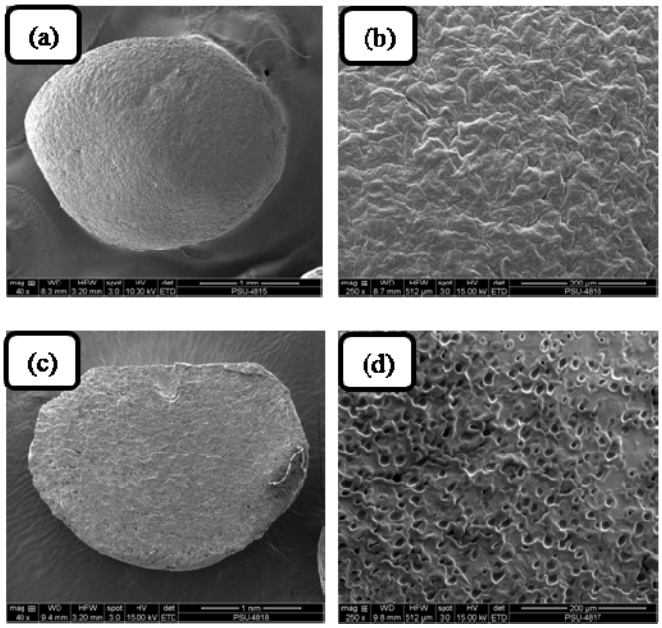


Fig. 2 SEM photographs of alginate beads (a) surface morphology (b) enlarged external structure (c) inner surface and (d) enlarged internal structure of the optimal floating alginate beads of curcumin

C. Determination of the Bead Buoyancy

Buoyancy studies of the curcumin floating alginate beads were carried out in 0.1 N HCl, pH 1.2, for a period of 8h. A preliminary study showed that the amount of oil had a significant influence on the bead buoyancy, and any oil concentrations lower than 10% w/w yielded non-floating alginate beads. All formula that contained 10% mineral oil and different amounts of surfactant could float without any lag time and remained buoyant over 8h. No significant signs of bead degradation were observed in the test medium.

D. Scanning Electron Microscopy (SEM)

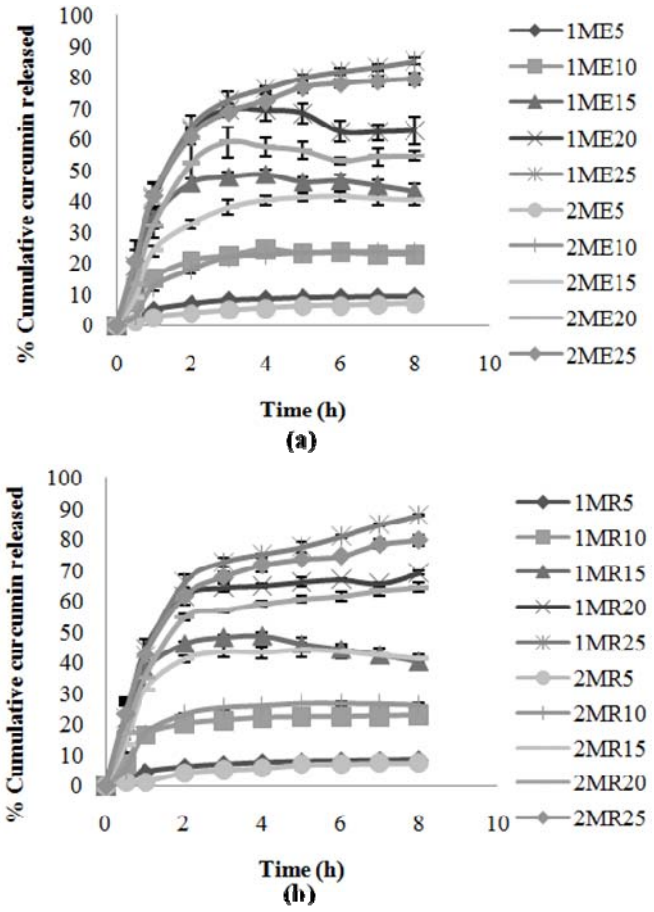
The external surface and cross-sectional morphologies of the optimal floating alginate beads containing 1% alginate, and 25% Cremophor RH, were observed by SEM. The external surface of the floating beads had an orange peel appearance with corrugations (Fig. 2 (a), (b)). No large crystals of drug were observed on the surface of these beads, signifying that the drug particles were in a delicately dispersed state within the sodium alginate matrix. The cross-sectional studies of the gel matrix showed a sponge like structure in which the oil was entrapped (Fig. 2 (c), (d)). The oil droplets were dispersed throughout the structure consequently they provided the ability to float.

E. In vitro Release of Curcumin from Floating Alginate Beads

The effect of the alginate concentration: When the amount of surfactant incorporated in the beads was constant, curcumin released from 2% alginate beads was lower than for the 1% alginate beads (Fig 3). An increase in the alginate concentration resulted in a lowering of the extent of the drug release. This could be due to retardation of the drug release property by the alginate polymer.

The effect of the amount of the surfactant: From Fig. 3 (a), the 1% alginate beads that were prepared with 25% Cremophor EL had a cumulative release of curcumin of about 85% in 8 h while the beads containing 5% Cremophor EL released less than 10% within 8h. In addition the trend of the drug release pattern of the beads prepared from Cremophor RH or Tween 80 was obvious in the same way as for the Cremophor EL beads. An increase in the concentration of the surfactant resulted in an increase in the extent of drug release. Formulations containing lower amounts of surfactant produced an incomplete solubilization of curcumin, whereas the curcumin was completely dissolved in the systems containing surfactants above 15%. Larger amount of surfactant therefore produced a higher drug release.

The effect of the type of surfactant: The cumulative drug release patterns of the floating alginate beads produced with different surfactants at a constant amount demonstrated that they were very similar. The drug release profiles of curcumin from the beads containing various types of surfactants were also related to the solubility of curcumin in each surfactant. Setthacheewakul et al. [21] previously had shown that Cremophor RH exhibited a better solubilizing capacity than Cremophor EL and Tween 80, respectively.



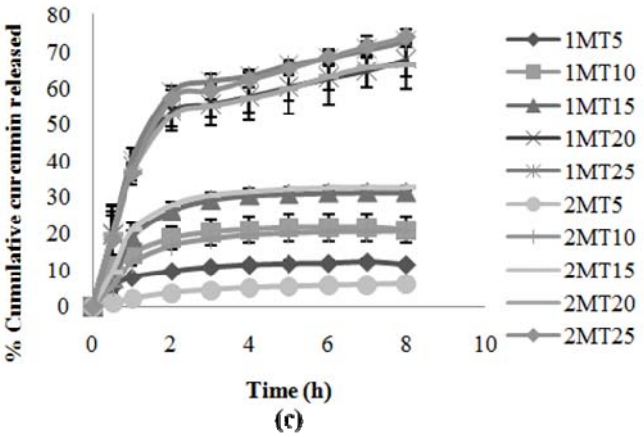


Fig. 3 Effects of alginate and surfactant on the release of curcumin from oil entrapped floating alginate gel beads: (a) Cremophor EL, (b) Cremophor RH (c) Tween 80. The mean ± SD of triplicate data are plotted

F. In Vitro Release of Curcumin from the Optimized Formulation

Floating alginate beads, containing 1% alginate and 25% Cremophor RH (1MR25), was the optimized formulation in this study. The drug release was about 65% within 2h and the total release was nearly 90%, while those of the curcumin beads without surfactant and curcumin powder were lower than 10% over an 8h period (Fig. 4).

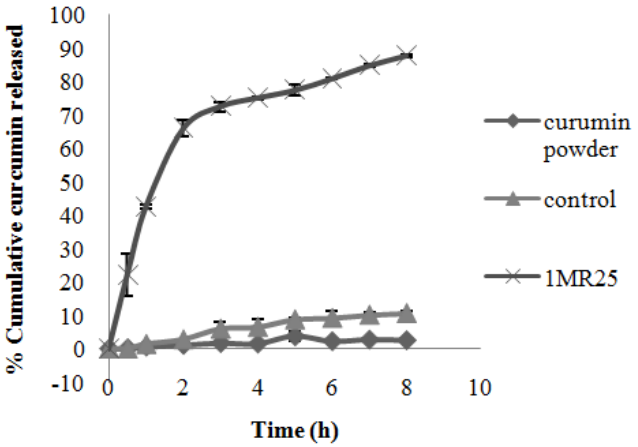


Fig. 4 Release profile of curcumin from the optimized formulation (1ME25) compared with the release from control beads (curcumin beads without surfactant), and curcumin powder in 0.1M HCl pH 1.2. The mean ± SD of triplicate data are plotted

IV. Conclusion

Floating alginate gel beads of curcumin based on an oil-loaded system were successfully prepared. The optimal formula containing 1% alginate, 10% mineral oil and 25% Cremophor RH had a good appearance, floating properties with instant buoyancy, and the floating duration was longer than 8h. About 90% of curcumin was released within 8h while the unformulated powder dissolved only 10% of curcumin in 8h. This study demonstrated the use of surfactants to improve

the solubility of curcumin, and with mineral oil to provide buoyancy of the delivery system.

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REFERENCES

[1] B. Gander, K. Ventouras, R. Gurny and E. Doelker. “In vitro dissolution medium with supramicellar surfactant concentration and its relevance for in vivo absorption,” Int. J. Pharm., Vol. 27, no. 1, pp. 117–124, Nov. 1985.

[2] P. Somparn, C. Phisalaphong, S. Nakornchai, S. Unchern and N. P. Morales. “Comparative antioxidant activities of curcumin and its demethoxy and hydrogenated derivatives,” Biol. Pharm. Bull., Vol. 30, no. 1, pp. 74-78, Jan. 2007.

[3] X. Wang, Y. Jiang, Y. Wang, M. Huang, C. Ho and Q. Huang. “Enhancing anti-inflammation activity of curcumin through O/W nanoemulsions,” Food. Chem., Vol. 108, no. 2, pp. 419-424, May. 2008.

[4] N. Chainani-Wu. “Safety and anti-inflammatory activity of curcumin: a component of tumeric (Curcuma longa),” J. Altern. Complement. Med., Vol. 9, no. 1, pp. 161-168, Feb 2003.

[5] K. J. Kim, H. H. Yu, J. D. Cha, S. J. Seo, N. Y. Choi and Y. O. You. "Antibacterial activity of Curcuma longa L. against methicillin-resistant Staphylococcus aureus," Phytother. Res., Vol. 19, no. 7, pp. 599-604, Jul. 2005.

[6] S. Mahattanadul, T. Nakamura, P. Panichayupakaranant, N. Phdoongsombut, K. Tungsinmunkong and P. Bouking. “Comparative antiulcer effect of bisdemethoxycurcumin and curcumin in a gastric ulcer model system,” Phytomedicine, Vol. 16, no. 4, pp. 342-351, Apr. 2009.

[7] U. M. Viradia, A. M. Shenoy, M. S. Rajan, A. R. Shabaraya, A. D. Kothadia and N. H. Patel. “Effect of leukotriene receptor antagonist montelukast along with curcumin against gastric ulceration,” Int. J. Pharm. Sci. Rev. Res., Vol. 3, no. 3, pp. 184-187, 2011.

[8] A. Goel, A. B. Kunnumakkara, B. B. Aggarwal. “Curcumin as "Curecumin": from kitchen to clinic,” Biochem. Pharmacol., Vol. 75, no. 4, pp. 787-809, Feb. 2008.

[9] P. Yoysungnoen, P. Wirachwong, C. Changtam, A. Suksamrarn and S. Patumraj. “Anti-cancer and anti-angiogenic effects of curcumin and tetrahydrocurcumin on implanted hepatocellular carcinoma in nude mice,” World. J. Gastroenterol., Vol.14, no. 13, pp. 2003-2009, Arp.2008.

[10] P. Anand, A. B. Kunnumakkara, R. A. Newman, B. B. Aggarwal. “Bioavailability of curcumin: problems and promises,” Mol. Pharm., Vol. 4, no. 6, pp. 807-818, Nov.-Dec. 2007.

[11] P. Ratanajiajaroen, M. Ohshima. “Synthesis, release ability and bioactivity evaluation of chitin beads incorporated with curcumin for drug delivery applications,” J. Microencapsul., Vol. 29, No. 6, pp. 549-558, 2012.

[12] S. Song, Z. Wang, Y. Qian, L. Zhang and E. Luo, "The release rate of curcumin from calcium alginate beads regulated by food emulsifiers," J. Agric. Food. Chem., Vol. 60, no. 17, pp. 4388-4395, May. 2012.

[13] S. Arora, J. Ali, A. Ahuja, R. K. Khar, and S. Baboota. “Floating drug delivery systems: a review,” AAPS Pharm. Sci. Tech., Vol. 6, no. 3, pp. E372–E390, Sep. 2005.

[14] A. D. Khan, M. Bajpai. “Floating drug delivery system: an overview,” Pharm. Tech., Vol. 2, no. 4, pp. 2497-2505, Oct-Dec 2010.

[15] B. N. Singh, K.H. Kim. “Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention,” J. Control. Release., Vol. 63, No. 3, pp. 235-259, Feb. 2000.

[16] Shishu, N. Gupta and N. Aggarwal. “Bioavailability enhancement and targeting of stomach tumors using gastro-retentive floating drug delivery system of curcumin—“a technical note”,” AAPS Pharm. Sci. Tech., Vol. 9, No. 3, pp. 810–813, Sep. 2008.

[17] A. K. Singhal, N. Nalwaya, E. E. Jarald and S. Ahmed. “Colon targeted curcumin delivery using guar gum,” Phcog. Res., Vol 2, no. 2, pp. 82-85, 2010.

[18] R. K. Das, N. Kasoju, U. Bora. “Encapsulation of curcumin in alginate-chitosan-pluronic composite nanoparticles for delivery to cancer cells” Nanomedicine., Vol. 6, no. 1, pp. 153-160, Feb. 2010.

[19] S. Mishra, K. Pathak. “Formulation and evaluation of oil entrapped gastroretentive floating gel beads of loratadine,” Acta. Pharm., Vol. 58, no. 2, pp. 187–197, Jun. 2008.

[20] I. Singh, P. Kumar, H. Singh, M. Goyal and V. Rana. “Formulation and evaluation of domperidone loaded mineral oil entrapped emulsion gel (MOEG) buoyant beads,” Acta. Pol. Pharm., Vol. 68, no. 1, pp. 121-126, Jan.-Feb. 2011.

[21] S. Setthacheewakul, S. Mahattanadul, N. Phadoongsombut, W. Pichayakorn, R. Wiwattanapatapee. "Development and evaluation of self-microemulsifying liquid and pellet formulations of curcumin, and absorption studies in rats,"Eur. J. Pharm. Biopharm., Vol. 76, no. 3, pp. 475-485, Nov. 2010.