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Formulation and Evaluation of Curcumin (SEDDS Emulsion) encapsulated in soft gelatin-coated capsule

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Abstract

The objective of the work was to utilize the colon-specific drug delivery for the treatment of cancer disease to achieve better therapeutic effects and lesser side effects. Colon-targeted drug delivery systems for curcumin were developed. Curcumin (CUR) microspheres were designed to control and target drug release to the colon. Drug delivery to colon encounters obstacle such as absorption and degradation in the upper GIT. The optimum drug delivery to colon requires avoidance of the absorption and metabolic breakdown of these drugs from the stomach and small intestine. Therefore, pH sensitive polymer Eudragit S 100 was chosen, which can bypass the upper GIT and can retain on the surface of colon ensures local and targeted effect.Curcumin can chelate various metal ions to form metal complexes of curcumin, which can show greater effects than curcumin alone. In this work the curcumin complex with zinc metal for its synergistic effect in cancer treatment.

Keywords

Self-Emulsification, Curcumin, *nano spheres, Curcumin*.

Introduction:

We all live in the kingdom of ill(s) and cancer is the immortal illness that enters in our mind due to its mysterious characteristics. It is amazing when we think that within our body all the bloody malignant cells are playing the game of uncontrolled replication (causing a bulging tumor(s)) and spreading in space, avoiding the existence of our strong immune system. And at the day's end our lives become vulnerable to this unpredictable threat. In the 21st century, Cancer is expected to rank as the leading cause of death related to noncommunicable diseases (NCDs), and at the same time, it will act as the most critical barrier to increasing life expectancy in every country. As per GLOBOCAN 2018 [1], a status report on the global burden of cancer worldwide, produced by the International Agency for Research on Cancer, with a focus on geographic variability across 20 world regions, there

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will be an estimated 18.1 million new cancer cases (17.0 million excluding nonmelanoma skin cancer) and 9.6 million cancer deaths (9.5 million excluding nonmelanoma skin cancer) in 2018 in both sexes combined. Among all types, lung cancer is the most commonly diagnosed cancer (11.6% of the total cases) and the leading cause of cancer death (18.4% of the total cancer deaths), closely followed by female breast cancer (11.6%), prostate cancer (7.1%), and colorectal cancer (6.1%) for incidence and colorectal cancer [2](9.2%), stomach cancer (8.2%), and liver cancer (8.2%) for mortality. The highest colon cancer incidence rates are found in parts of Europe (eg, in Hungary, Slovenia, Slovakia, the Netherlands, and Norway), Australia/New Zealand, Northern America, and Eastern Asia (Japan and the Republic of Korea, Singapore [in females]), with Hungary and Norway ranking first among males and females, respectivelyWe all live in the kingdom of ill(s) and cancer is the immortal illness that enters in our mind due to its mysterious characteristics. It is amazing when we think that within our body all the bloody malignant cells are playing the game of uncontrolled replication (causing a bulging tumor(s)) and spreading in space, avoiding the existence of our strong immune system. And at the day's end our lives become vulnerable to this unpredictable threat. In the 21st century, Cancer is expected to rank as the leading cause of death related to noncommunicable diseases (NCDs), and at the same time, it will act as the most critical barrier to increasing life expectancy in every country. As per GLOBOCAN 2018 [1], a status report on the global burden of cancer worldwide, produced by the International Agency for Research on Cancer, with a focus on geographic variability across 20 world regions, there will be an estimated 18.1 million new cancer cases (17.0 million excluding nonmelanoma skin cancer) and 9.6 million cancer deaths (9.5 million excluding nonmelanoma skin cancer) in 2018 in both sexes combined. Among all types, lung cancer is the most commonly diagnosed cancer (11.6% of the total cases) and the leading cause of cancer death (18.4% of the total cancer deaths), closely followed by female breast cancer (11.6%), prostate cancer (7.1%), and colorectal cancer (6.1%) for incidence and colorectal cancer [2](9.2%), stomach cancer (8.2%), and liver cancer (8.2%) for mortality. The highest colon cancer incidence rates are found in parts of Europe (eg, in Hungary, Slovenia, Slovakia, the Netherlands, and Norway), Australia/New Zealand, Northern America, and Eastern Asia (Japan and the Republic of Korea, Singapore [in females]), with Hungary and Norway ranking first among males and females, respectively.

MATERIALS AND METHODS

MATERIALS

Curcumin was received as a gift sample from Asoj Soft Caps Private Limited Halol - Vadodara Rd, Halol, Khandiwada, Gujarat, India. Chitosan (low mol. wt., viscosity 20-200 cP) and Eudragit S100 (Evonik Rohm Pharma, Germany, Viscosity 50–200 mPa s, mol. wt. 135,000) were received as a gift

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sample from Matrix laboratory, Hyderabad. The deacetylation degree of chitosan according to the specifications from the provider was higher than 80%. Span 80 (Mol. wt. 428.6, viscosity 1200-2000 mPa s) and liquid paraffin, anhydrous zinc chloride, carboxy methyl cellulose were purchased from Loba chemie Mumbai, India. All chemicals and reagents used were of analytical grade. Double distilled water was used throughout the study.

METHOD

Experimental

Preparation of Curcumin (SEDDS Emulsion) encapsulated in soft gelatin-coated capsule

Preparation of SEDDS of Curcumin (SEDDS)

Emulsion cross-linking method:

Chitosan polymer was dissolved in 10 mL of aqueous solution of acetic acid (1%) and Curcumin (SEDDS) was dispersed in the polymeric solution (Table 3.2). This solution was added to 100 ml of liquid paraffin containing Span 80 (1% v/v). A w/o emulsion was formed by stirring at 1500 rpm for 2 h with the help of a mechanical stirrer (Remi Motors, Mumbai, India). 0.5 ml of glutaraldehyde was added to the emulsion and kept for 1 h. The solvents were removed by stirring under a vacuum. SEDDS were obtained by filtration, washed with petroleum ether, and dried in a hot air oven at 40º C. All the studies were performed in amber-colored glass apparatus and under dark conditions.

Preparation of capsules consisting non-aqueous SENE:

A previously formulated emulsion was filled into soft gelatin capsules for easy oral drug delivery and further characterized by a liquidized self-emulsifying nano emulsion. This filling was carried out using the Rotary die process method as mentioned below in Asoj Soft Caps Private Limited, Vadodara, Halol, Gujrat.

Rotary Die process: The two sides of a capsule are concurrently created from two ribbons of gelatin that are continually fed into a rotating die assembly. Near a filling injector, the ribbons come together. A pump that measures and delivers the correct volume of fill material into the capsules activates the fill injector. As the die assembly rotates, the filled capsules are then sealed. This method enables precise and repeatable fill uniformity. After encapsulation, the capsules are dried in a tumble dryer that uses a lot of pushed air and at a high temperature. The capsules are put onto trays and put into a low-humidity drying room after leaving the drying tunnel.Major bioactive compounds in lemongrass

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oil

Coating of Eudragit polymer on capsules:

Polymer coating of Eudragit RS100 onto the capsules is done by using a pan coating method.Soft gelatin capsules were coated in a pan-coater (GlattR GC-300, Glatt, Binzen, Germany) with Eudragit RS100 inisopropyl alcohol and acetone (1:1). The coating conditions were: batch size, 1.2 kg; prewarming of the capsules at 30 ℃ for 30 min before coating;) air flow rate, 130 m3 /h; pneumatic spraying pressure, 1.2 bar; spray rate, 5 –7 g/min; spray nozzle diameter, 1.2 mm; pan rotation speed, 15 rpm.

Results and Discussion

Table 1: Percentage Yield, Entrapment efficiency, Drug content and contentuniformity of different batches of floating SEDDS.

S.no	Percentage Yield	Entrapment efficiency (% w/w)	Drug content	Content uniformity
1	63.28	58.52	64.60	63.75
2	63.43	60.58	63.6	64.11
3	61.23	63.86	64.25	62.87
4	61.02	69.50	65.46	66.89
5	62.64	55.85	63.12	67.12
6	62.57	61.70	65.86	62.86
7	61.28	65.52	62.60	65.75
8	61.43	70.58	66.56	64.11
9	62.23	59.86	64.25	66.87
10	62.57	62.50	62.46	62.89

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11	60.64	64.85	63.12	63.12
12	60.57	68.70	62.86	66.86

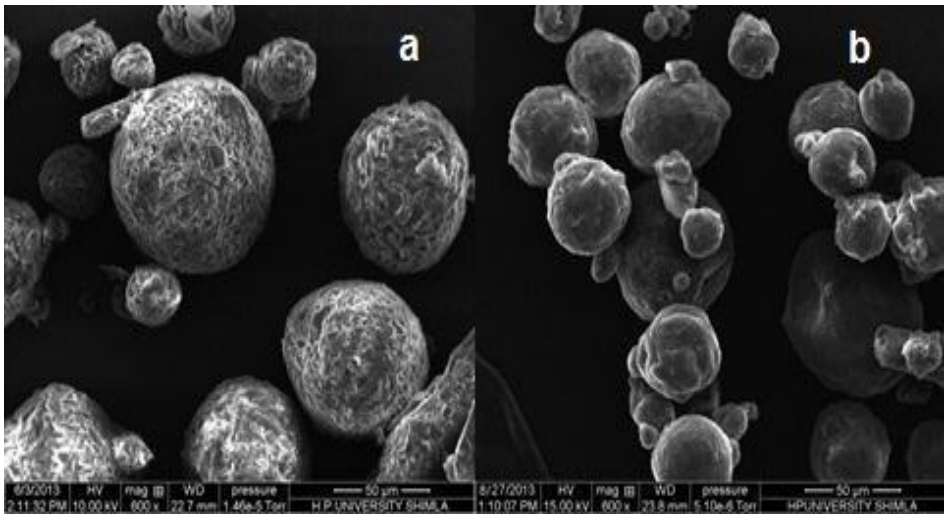

Fig. 1: (a) SEM image of CUR- chitosan SEDDS, (b) SEM image of Eudragit coated SEDDS

Table 2: Compilation of the evaluation parameters of CUR-loaded SEDDS

Formulation Code	Average particle size (µm)	Degree of Swelling* (Mean ± S.D)	Percentage Yield (%)* (Mean ± S.D)	Drug Loading (%)*(Mean ± S.D)	Encapsulation Efficiency (%)* (Mean ± S.D)
F1	36.84	12.34 ± 0.98	82.36 ± 0.84	38.17 ± 0.25	74.69 ± 0.25
F2	44.96	18.49 ± 1.07	81.25 ± 0.16	26.97 ± 0.49	78.23 ± 0.47
F3	60.05	22.86 ± 0.79	83.64 ± 0.49	21.11 ± 0.74	80.61 ± 0.39
F4	77.25	24.13 ± 0.62	85.43 ± 0.94	16.46 ± 0.37	82.50 ± 0.71
F5	93.27	10.94 ± 0.16	86.22 ± 0.83	40.59 ± 0.27	73.88 ± 0.54
F6	105.40	17.51 ± 0.55	87.75 ± 0.59	29.74 ± 0.18	76.65 ± 0.20
F7	121.37	20.77 ± 0.84	86.36 ± 0.37	21.66 ± 0.97	81.42 ± 0.85
F8	129.74	23.37 ± 0.84	88.87 ± 0.42	17.26 ± 0.75	83.37 ± 0.62

*n=6, mean± SD

***In-vitro* drug release**

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In-vitro release studies of CUR-loaded SEDDS were performed in simulated GI fluidsusing USP dissolution (type-I) test apparatus in 900 ml of the dissolution medium, stirred at 50 rpm at 37 ± 0.5°C. The *in-vitro* release profiles of various batches were performed using three different dissolution media to mimic the GI conditions and the results are shown in Table 3 & 4. Fig. 2 & Fig. 3 shows the *in-vitro* release profiles of drug from chitosan SEDDS and Eudragit coated chitosan SEDDS. The *in-vitro* release studies of F6 formulation were also performed in presence of rat caecal contents and pepsin to simulate the GIT environment and the results are shown in Table 3 & Fig 4.

Table 3: *In-vitro* drug release of CUR-loaded chitosan SEDDS (F1-F4)

Time (h)	% Cumulative Drug Release*			
	F1	F2	F3	F4
0	0	0	0	0
1	3.65±0.72	2.1±0.14	1.69±0.35	0.48±0.09
2	9.57±0.61	7.47±0.78	6.72±0.45	5.53±0.31
3	14.14±0.68	12.78±0.98	10.32±0.65	10.79±0.54
4	20.25±0.87	18.12±0.58	16.77±0.59	15.97±0.64
5	22.98±0.58	20.89±0.59	19.65±0.74	19.12±0.61
6	27.46±1.2	25.12±0.67	22.79±0.88	20.27±0.74
7	29.74±0.35	26.36±0.81	24.12±0.64	21.96±0.85
8	32.23±0.87	27.97±0.97	25.6±0.81	22.83±0.38
9	34.14±0.59	29.47±0.98	27.23±0.97	25.12±0.46
10	35.97±0.64	31.74±0.85	29.91±0.64	27.96±0.57
11	36.55±0.78	33.78±0.76	30.25±0.73	29.45±0.28
12	36.91±0.89	34.14±0.66	32.57±0.95	29.85±0.34

*n=6, mean± SD

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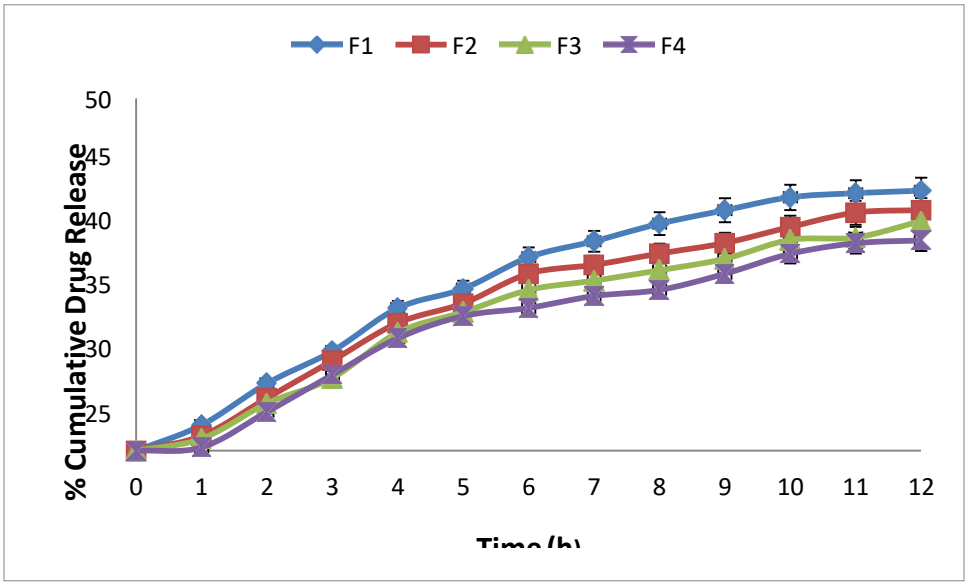

Fig.2: In-*vitro* release profile of CUR loaded chitosan SEDDS showing burst release at stomach pH (F1-F4)

Table 4: *In-vitro* drug release of Eudragit coated CUR-loaded chitosan SEDDS(F5-F8)

Time (h)	% Cumulative Drug Release*			
	F5	F6	F7	F8
0	0	0	0	0
1	3.96±0.26	3.62±0.34	3.05±0.37	2.68±0.25
2	5.9±0.29	5.08±0.39	4.23±0.39	3.55±0.34
3	6.72±0.34	6.15±0.42	5.17±0.45	4.84±0.39
4	8.63±0.38	7.22±0.49	6.55±0.58	5.37±0.41
5	11.52±0.47	10.25±0.51	8.69±0.98	7.52±0.49
6	21.45±0.97	15.45±0.87	12.35±0.48	10.08±0.57
7	29.36±0.59	23.77±0.64	21.43±0.67	16.36±0.59
8	32.78±0.67	29.56±0.58	27.6±0.91	25.79±0.64
9	36.12±0.73	32.34±0.84	30.72±0.57	27.61±0.67
10	39.36±0.69	35.87±0.49	33.96±0.24	29.25±0.49
11	40.64±0.88	36.47±0.74	34.28±0.18	30.4±0.59
12	41.85±0.59	37.53±0.58	35.53±0.97	31.83±0.47

*n=6, mean± SD

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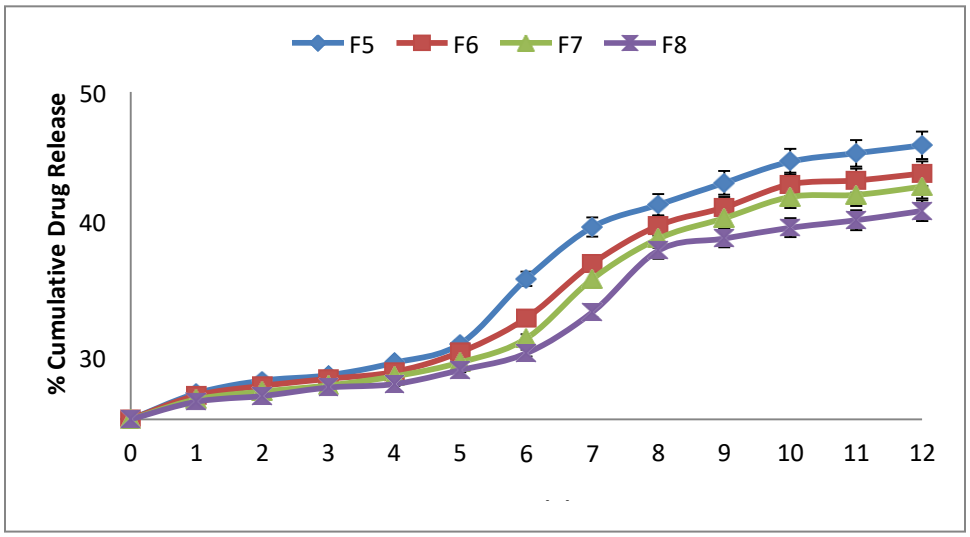

Fig. 3: Percent cumulative drug release from Eudragit S-100 coated CUR-chitosan SEDDS showing delayed release at colonic pH (F5-F8)

Table 5: *In-vitro* drug release of F6 with & without RCC and Pepsin

Time (h)	% Cumulative Drug Release (F6)*	
	Without RCC and Pepsin	With RCC and Pepsin
0	0	0
1	3.62±0.34	3.78±0.26
2	5.08±0.39	5.21±0.45
3	6.15±0.42	6.56±0.65
4	7.22±0.49	7.19±0.59
5	10.25±0.51	12.25±0.49
6	15.45±0.87	19.96±0.87
7	23.77±0.64	28.84±0.76
8	29.56±0.58	34.73±0.48
9	32.34±0.84	39.55±0.61
10	35.87±0.49	42.19±0.82
11	36.47±0.74	44.64±0.77
12	37.53±0.58	46.95±0.88

*n=6, mean± SD

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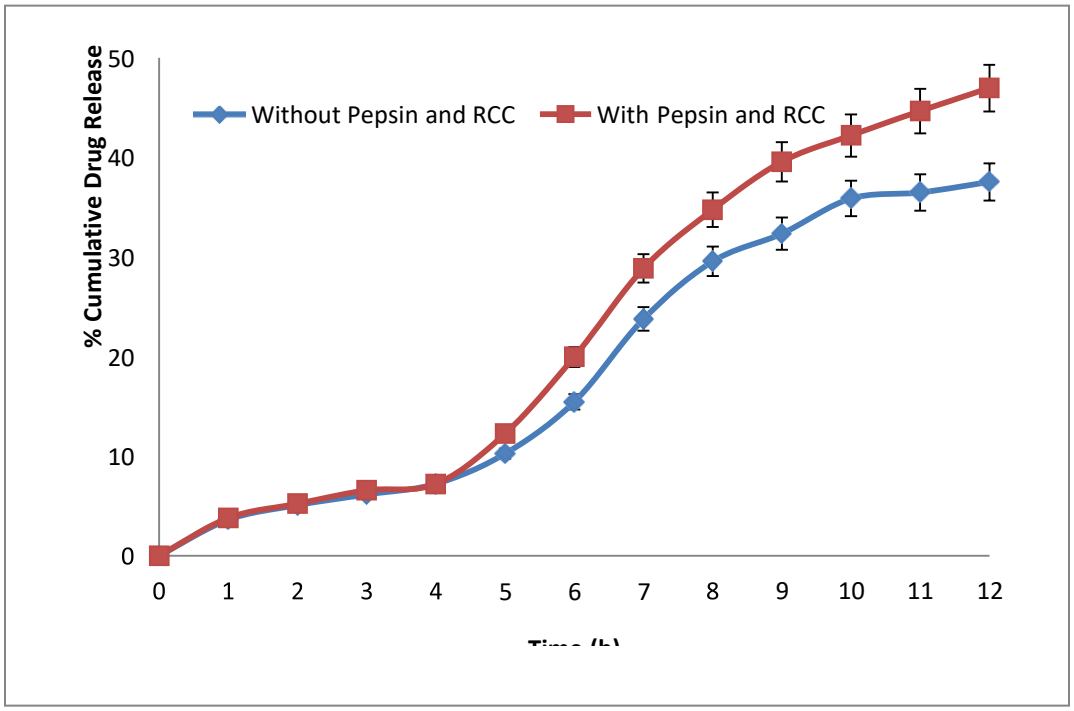

Fig. 4: Comparative *in-vitro* release profile of F6 with and without pepsin and rat caecal content (RCC) showing significant influence of RCC on drug release

Conclusion

Chitosan microspheres and Eudragit-coated chitosan microspheres of curcumin were prepared by the emulsion cross-linking method. These prepared microspheres were also evaluated for their various quality control parameters. The formulated microspheres were examined for particle size, shape, surface morphology, percentage yield, drug loading, entrapment efficiency (EE) and degree of swelling.

SEM photomicrograph of chitosan microspheres indicated that the cross-linked chitosan microspheres exhibited rough surface and spherical shape while SEM photomicrograph of Eudragit coated chitosan microspheres revealed smooth and spherical. The size of microspheres was found to increase (36.84µm to 77.25µm) with increase in chitosan concentration. Further the coating with Eudragit also showed significant increase in the size of microspheres. The mean particle size of the coated microspheres increased from 93.27µm to 129.74µm, which may be dueto the corresponding increase in the chitosan concentration that resulted in larger emulsion droplets.

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