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Cross-linked natural gum microspheres: a feasible attitude for boosting the delivery of dicyclomine hydrochloride

Ayan KR Kar, Pratik Samanta, Banhishikha Kar and Rana Majumdar

Abstract
Microspheres are fundamentally free-flowing powders consisting of a biodegradable polymer matrix where an active therapeutic agent dispersed uniformly within the matrix system and the loaded drug released in a controlled manner over a long period. As a modern drug-captured delivery tool, controlled drug delivery system released the entrapped drugs at the target site in a controlled manner. The focus of the present investigation is to design a microsphere formulation based on the drug-polymer ratio. Other parameters related to the formulation kept constant. Dicyclomine hydrochloride loaded guar gum-based microsphere was accomplished by ionotropic gelation method and characterized by different process parameters like particle size, entrapment efficiency etc. The compatibility study of drug with formulation components was confirmed by differential scanning calorimetry and fourier transform infrared study. The particle size increased with enhancing the amount of guar gum. *In vitro* release profile was done using USP dissolution apparatus II in different pH media which was found to be a pH-sensitive profile after 12 h. The release kinetics was fitted with zero-order kinetics and case II transport system according to the Korsmeyer-Peppas model. The present study introduces an approach for the fabrication of microspheres for prolonged release of Dicyclomine hydrochloride and it can be used effectively as a drug targeting delivery tool with increased therapeutic efficacy.

Keywords: Dicyclomine hydrochloride, Guar gum, sodium alginate, Ionotropic gelation method, microspheres.

Introduction
Novel drug delivery system means of improving the therapeutic effectiveness of incorporated drugs by providing controlled delivery, targeting and sustained delivery. The drugs into dosage form to sustain drug levels and hence drug action is obtained for a prolonged period in body. There has been an impressive development in the field of novel drug delivery systems. Carrier technology is an approach for drug delivery by the combination of the drug to a carrier particle such as microspheres, liposome, etc. that regulates the release characteristics of the drug at a fixed rate for a prolonged period [1, 2]. The colon is located at the end of the digestive tract, between the cecum and the rectum. The key technique for designing successful oral colon-targeted drug delivery systems (OCTDDS) is to choose the appropriate carrier system, which carefully releases a drug substance to the colonic environment by protecting from the upper gastrointestinal tract (GIT). Therefore, it is necessary to consider the physiological properties of the colon and the atmosphere of the neighbouring disease site (s) for the successful evolution of colon-targeted drug delivery systems [2, 3]. Different types of approaches have been used to achieve colon targeting which is either drug-specific (prodrug) or formulation specific (coated or matrix preparation). The most commonly used targeted mechanism is pH or time-dependent and enzyme activated drug delivery systems by using natural and synthetic polymers. However, a drug delivery system, which will be protected at upper GI conditions and specifically break down in contact with colonic pH in presence of the bacterial enzymes that are predominantly present in the colon, are more logical approach than the others due to less inter-individual variability [4, 5]. Microspheres are multi-particulate drug delivery systems which are ready to obtain prolonged or controlled drug delivery to improve bioavailability, stability and to target the drug to a specific site at a predetermined rate. They are made from polymeric waxy or other protective materials such as organic, semi-synthetic and synthetic polymers. Microspheres are characteristically free-flowing powders having a particle size ranging from 1-1000 µm consisting of techniques for the preparation of microspheres provides multiple options to control as a drug, administrative aspects and to enhance the therapeutic

efficacy of a given the drug. These delivery systems offer numerous advantages compared to conventional dosage forms, which include improved efficacy, reduced toxicity, improved patient compliance and convenience. Such systems often use macromolecules as carriers for drugs [6-8]. Being an anticholinergic drug, Dicyclomine hydrochloride (DCL) has smooth muscle relaxant action and also it gives antispasmodic action. Chemically, it is 2 - diethyl aminoethyl bicyclohexyl-1-carboxylate hydrochloride (Fig. 1) classified as BCS class I drug whose peak plasma concentration is achieved after 60-90 min of oral administration and approximately 4 to 6 hours is its plasma half-life. Generally, DCL is used to manage irritable bowel syndrome and also helps to cure the cramps of stomach, bladder and intestine. The use of DCL as an OCTDDS would be convenient due to depletion of systemic side effects, increasing patient compliance by lightening the dosing frequency and improving the therapeutic outcomes [9-13]. In the present investigation, the main aim is to design a successful delivery system to the target cell requires protection of the drug from degradation or release in the stomach and then gives controlled release of the drug.

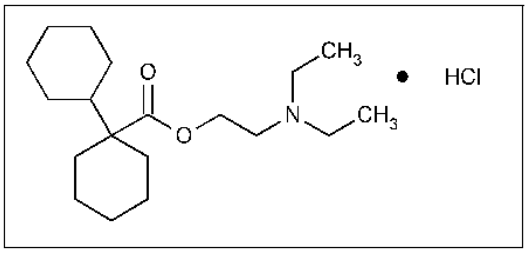

Fig 1: Structure of Dicyclomine Hydrochloride.

Materials and methods

Materials

Dicyclomine hydrochloride (Life pharmaceutical Pvt. Ltd, India), guar gum, sodium alginate, calcium chloride (Merck Specialities Private Limited, India) and glutaraldehyde (Loba Chemie, India) were used for the present investigation. All other chemicals were commercially available and of analytical grade.

Methods

Fourier transform infrared spectroscopy (FTIR) study

Compatibility study between the active pharmaceutical ingredient (API) and excipients must be established to produce a stable, efficacious, attractive and safe product. The API and physical mixture were subjected for FTIR (Spectrum-100, UK) analysis scanned over a range of 4000-400cm-1 to confirm any presence of cross-linking [14].

Differential scanning calorimetry (DSC) study

DSC study was analyzed on DCL and the physical mixture of DCL and polymer using TA DSC 25 analyzer. Samples (approximately 2-3 mg) were put down in aluminium pans and sealed. After running over temperature range 40-450C, the thermogram of respective samples was recorded [14].

Preparation of guar gum-based microspheres

Guar gum-based microsphere was prepared by ionotropic gelation method using different drug-polymer ratio. Guar gum was dissolved separately at different concentration in cold water by exciting overnight to form a gelatinous solution. Sodium alginate was mixed properly with purified water. Then the pure drug was diffused into the gum solution and it was added to the sodium alginate solution with stirring to get a viscous form [14, 15]. 1 mL of glutaraldehyde [16] was added to the drug-loaded guar gum-based solution followed by uninterrupted stirring. The developing solution was added dropwise using a preselected sterilized syringed from a fixed height into the calcium chloride solution (5%) using magnetic stirrer with 400 rpm at a constant temperature of 50^0C. The established beads were preserved in the calcium chloride solution for 10-15 minutes to complete the formation of spherical rigid microspheres. Then it was filtered using filter paper and allowed to dry at room temperature.

Particle size analysis

Particle size analysis of prepared microsphere was resolved by the sieving method that separated into different size fraction depending on their particle size. The weighted microspheres were spread on the top of the sieve shaker (Geologists Syndicate Pvt Ltd, India) containing different sizes of sieve starting from # 12 to # 30. The mean particle size of all formulations was calculated using the following formula [15]

$$PSm = \sum (Fm \times Fw) \div \sum Fw \quad .....(1)$$

Where *PSm*, *Fm* and *Fw* indicate the mean particle size, mean particle size of the fraction and weight fraction respectively.

Estimation of drug loading capacity and encapsulation efficiency

Drug loading capacity, the maximal amount of drug that can be absorbed in the microspheres was determined to be the maximum amount of DCL found in 100 mg of microspheres. Encapsulation efficiency is the quantity of attached drug (in percent) that is encapsulated in the prepared microspheres. Encapsulation efficiency was calculated in terms of the ratio of the drug in the final formulation to the amount of added drug. Specific amount (100 mg) of the prepared microsphere was dispersed in the specific amount of previously prepared phosphate buffer at pH 7.4 and sonicated by the probe sonicator for 15 minutes. The solution was filtered by the whatman filter paper after 24 hours and assayed by UV spectrophotometer at 217 nm [17]. The outcome of % DCL loading and encapsulation was calculated by the respective equations and complied.

$$DL\ (\%) = (Dw / Mw) \times 100 \quad .....(2)$$

$$EE\ (\%) = (La / Lt) \times 100 \quad ..... \quad (3)$$

Where, *DL(%)*, *Dw* and *Mw* indicates the percentage of drug loading, weight of drugs in microsphere and weight of microsphere respectively in equation (2) and equation (3), *EE(%)*, *La* and *Lt* is the percentage of encapsulation efficiency, actual loading and theoretical loading respectively.

Evaluation of swelling behavior

A weighted quantity (100 mg) of prepared microsphere from all batches was positioned in simulated gastric fluid (0.1 N HCl at 1.2) followed by 10 h in phosphate buffer 7.4 and allowed to swell up to a constant weight. The swollen microspheres were removed, blotted with filter paper and a change in their weight was measured. The same process was

continued three times and the average value was reported. The degree of swelling (α) was calculated from the respective equation (4) [18, 19].

$$\alpha = \{(Wo - Wi) / Wi\} X\ 100 \text{ .....} (4)$$

Where *Wo* and *Wi* is the Final weight of swollen microsphere in medium and dry weight of microsphere respectively.

Scanning electron microscopy (SEM)

The surface morphology of drug-loaded microspheres was recorded by SEM (FEI Quanta-200 MK2, Netherland) analysis after coating with gold/platinum under vacuum [20].

***In-vitro* drug release studies**

In-vitro drug release study was carried out using USP dissolution apparatus (LabIndia, Mumbai, India) furnished with six baskets. The dissolution rate was firmed at 37±0.50C in 900 ml of 0.1N HCl with 50 rpm for first 2 h; the medium was replaced with simulated intestinal fluid at pH 6.8 for next 3 h followed by phosphate buffer at pH 7.4 until the microspheres will be dissolved completely. An aliquot of the sample (5ml) was withdrawn at a systematic time interval and replaced the same amount of fresh medium into the vessel to maintain sink condition throughout the experiment. The collected sample was then analyzed by the UV spectrophotometrically (Shimadzu UV-1700) at respective wavelength [19, 20]. Each drug release experiment was replicated three times (n=3).

Analysis of release kinetics and mechanism

In-vitro release data were fitted with different release kinetics models [21, 22]

Zero-order model: $Q = kt + Q0$ ……... (5)
First-order model: $Q = Q0e^{k-t}$ ……. (6)
Higuchi model: $Q = k\sqrt{t}$ ……..... (7)
Korsmeyer Peppas model: $Q = ktn$ …. (8)

Where Q represents the drug released amount in time t and Q0isthe start value of Q; k is the rate constants; n is the release exponent.

The release data were fitted to different models and its regression values range from 0.992 to 0.998 as its value nearer to the '1' it is conformed as it follows the slow first-order release. Different n values of the Korsmeyer-Peppas equation indicate a different mechanism of drug release. The mechanism of drug release is further confirmed by the Korsmeyer-Peppas plot, if n=0.45 it is called case I or Fickinan diffusion, $0.45 < n < 0.89$ is for anomalous behaviour or non-Fickian transport.

Statistical analysis

All measured data are expressed as mean ± standard deviation (S.D.) where N is the number of the data point equal to 3.

Result and discussion

FTIR study

The FTIR study of DCL and the physical mixture of DCL were studied to verify the identity of the sample. A pellet of around 1mm diameter of the sample was prepared by compression technique and scanned between 4000-1 – 400 cm-1 using a FTIR (Spectrum-100, UK). In Fig. 2, FTIR spectrum of DCL revealed at 1133.1 cm-1 (C-N stretching), 1192.7 cm-1 (C-O stretching), 1714.6 cm-1 (C=O [ester] Stretching) and 2926.0 cm-1 (C-H Stretching). All the data was indicating the absence of any kind of physical and chemical interaction between DCL and the polymer blend.

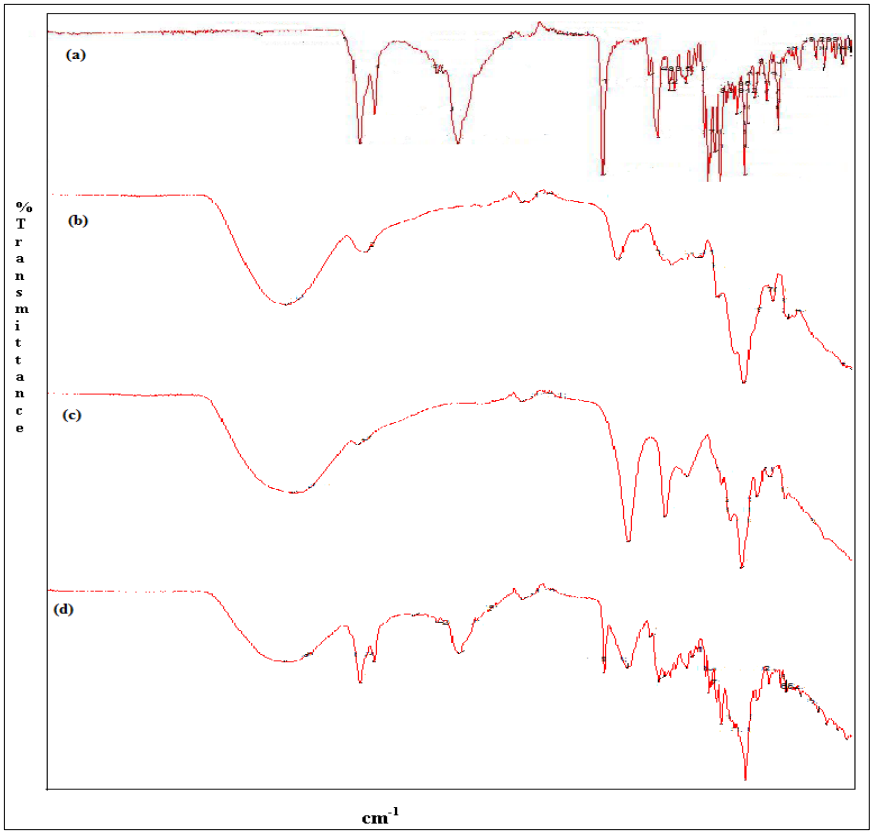

Fig 2: FTIR Spectra of (a) DCL (b) Guar Gum (c) Sodium Alginate (d) Physical mixture.

DSC study

In the present study (Fig. 3), it was observed that there is a sharp peak at 176.660C in the thermogram of DCL which indicates to the melting point of a drug in the crystalline form. The characteristic peak of DCL and polymer physical mixture was also observed which suggested that there was no interaction between the DCL and polymer used.

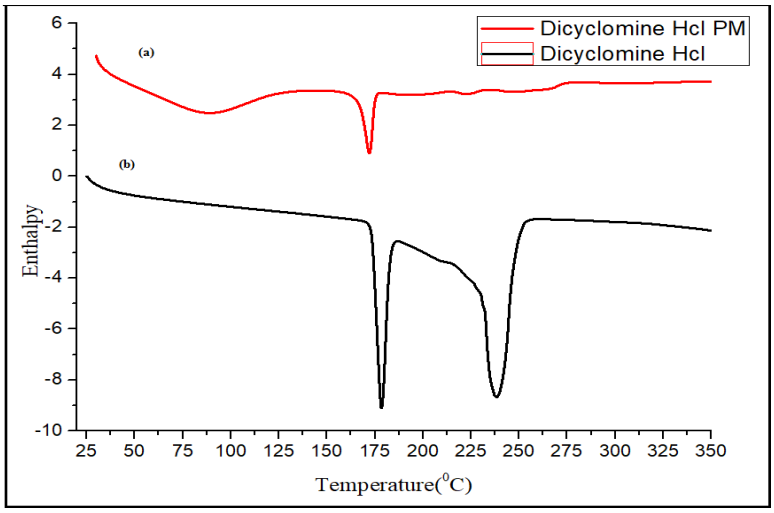

Fig 3: DSC Study (a) Physical Mixture of DCL and Polymers and (b) DCL.

Design of gum-based microspheres

DCL loaded microsphere was designed using a different ratio of drug-polymers shown in Table 1. Different formulation variables like stirring speed 400 rpm, the temperature of the system at 40ºC, needle diameter, 23 G and stirring time for 4hrs that may influence the composing and properties of the microspheres were recognized and keeping constant. Calcium alginate coat bordering the beads were formed by crosslinking of alginate molecules with calcium ions of calcium chloride solution and that may be interfered by the increasing amount of gum. As the quantity of gum increased the viscosity of solution also increases resulting in increased particle size.

Table 1: Formulation ratio of DCL loaded gum based microspheres.

Formulation code	Drug (mg)	Guar gum (mg)	Sodium alginate (mg)	Total Polymer (mg)	Drug: polymer ratio	Glutaraldehyde (ml)
F1	60	12	48	60	1:1	_
F2	60	36	84	120	1:2	_
F3	60	72	108	180	1:3	_
F4	60	120	120	240	1:4	_
F5	60	12	48	60	1:1	1.0
F6	60	36	84	120	1:2	1.0
F7	60	72	108	180	1:3	1.0
F8	60	120	120	240	1:4	1.0

Particle size analysis

The particle size of DCL loaded microsphere of various formulations was determined by sieving method shown in Table 2. The mean diameter of Guar gum crosslinked with Glutaraldehyde microspheres was found to be increased from 420 ± 0.72 µm to 533±0.29 µm. The average particle size of microspheres increased with increasing polymer as well as the cross-linking agent. of prepared microspheres presented in Table 3 was increased up to 79.81 ± 1.61% with an increasing polymer concentration of Guar gum and ranges from 12.96 ± 0.17% to 18.78 ± 0.28% of the microsphere with increasing the amount of polymer as well as cross-linking agent respectively. It was also observed that the cross-linking agent (Glutaraldehyde) also affected the encapsulation efficiency with an increasing amount of glutaraldehyde up to 1%.

Table 2: Particle size analysis of prepared microspheres.

S. No.	Formulation code	Mean particle size µm(±S.D)
1.	F1	420 ±0.72
2.	F2	480± 0.56
3.	F3	500± 0.59
4.	F4	504±0.41
5.	F5	434± 0.69
6.	F6	502±0.57
7.	F7	507±0.30
8.	F8	510±0.29

Table 3: Drug loading and encapsulation efficiency analysis.

S. No.	Formulation code	DEE %	DL %
1.	F1	80.81 ±1.61	19.78 ± 0.28
2.	F2	70.23 ±2.56	13.49 ± 0.25
3.	F3	78.16 ±2.59	16.89 ± 0.34
4.	F4	78.37 ±2.24	18.51 ± 0.30
5.	F5	79.69 ±2.22	18.56 ± 0.17
6.	F6	74.93 ±2.48	15.18 ± 0.30
7.	F7	57.66 ±2.45	12.96 ± 0.17
8.	F8	75.82 ±2.75	16.44 ± 0.40

Drug loading capacity and encapsulation efficiency analysis

The result of DCL encapsulation efficiency and drug loading

Swelling behavior

The % swelling index of various formulations in water, 0.1N HCl, phosphate buffer at 6.8 and 7.4 was presented in Table

4. It was observed that the swelling index of prepared microspheres in acidic medium (0.1N HCl) was lower in comparison with that of in alkaline medium. This study was specifying a pH-sensitive swelling behaviour which may arise due to shrinkage of alginate at acidic pH.

Table 4: Swelling study of DCL loaded microspheres.

S. No.	Solvent	F1	F2	F3	F4	F5	F6	F7	F8
1.	0.1N HCl	94	87	86	92	175	89	99	183
2.	Phosphate buffer 6.8	151	161	110	211	189	114	242	181
3.	Phosphate buffer 7.4	186	148	198	268	289	365	202	232

In-vitro release kinetics

In Vitro DCL release profile from various formulations is presented in Fig. 4. The release profile was analyzed in 0.1N HCl for first 2 h; the buffer was replaced with simulated intestinal fluid at 6.8 for next 3 h followed by phosphate buffer at pH 7.4. The temperature, rotation speed and other parameter related to the study were kept constant. The drug-loaded prepared microsphere was found to be sustained over 12 h. During this stage, it was observed that the drug release study was found to be quite faster in simulated intestinal fluid and alkaline solution comparatively than the acidic medium. This might be happened due to the high swelling rate in alkaline solution.

Release kinetics

In vitro release data of prepared DCL loaded microsphere was subjected into various kinetics model like zero order, first order, Higuchi model and Korsmeyer-Pappas model graphically (Fig. 4) and mathematically to understand the release behaviour of the drug. Correlation coefficients (r^2) of different formulations shown in Table 5 was calculated and compared. The drug release from the formulations was found to be best fitted by the zero-order kinetic model which implies that the drug release from the DCL loaded microspheres was in a controlled manner throughout the release study and it is a dissolution-controlled system. The release exponent (n) was also determined. According to the Korsmeyer-Peppas model, it was found to follow super case II transport controlled by the swelling that might be assigned due to the dissolution process and polymer chain relaxation.

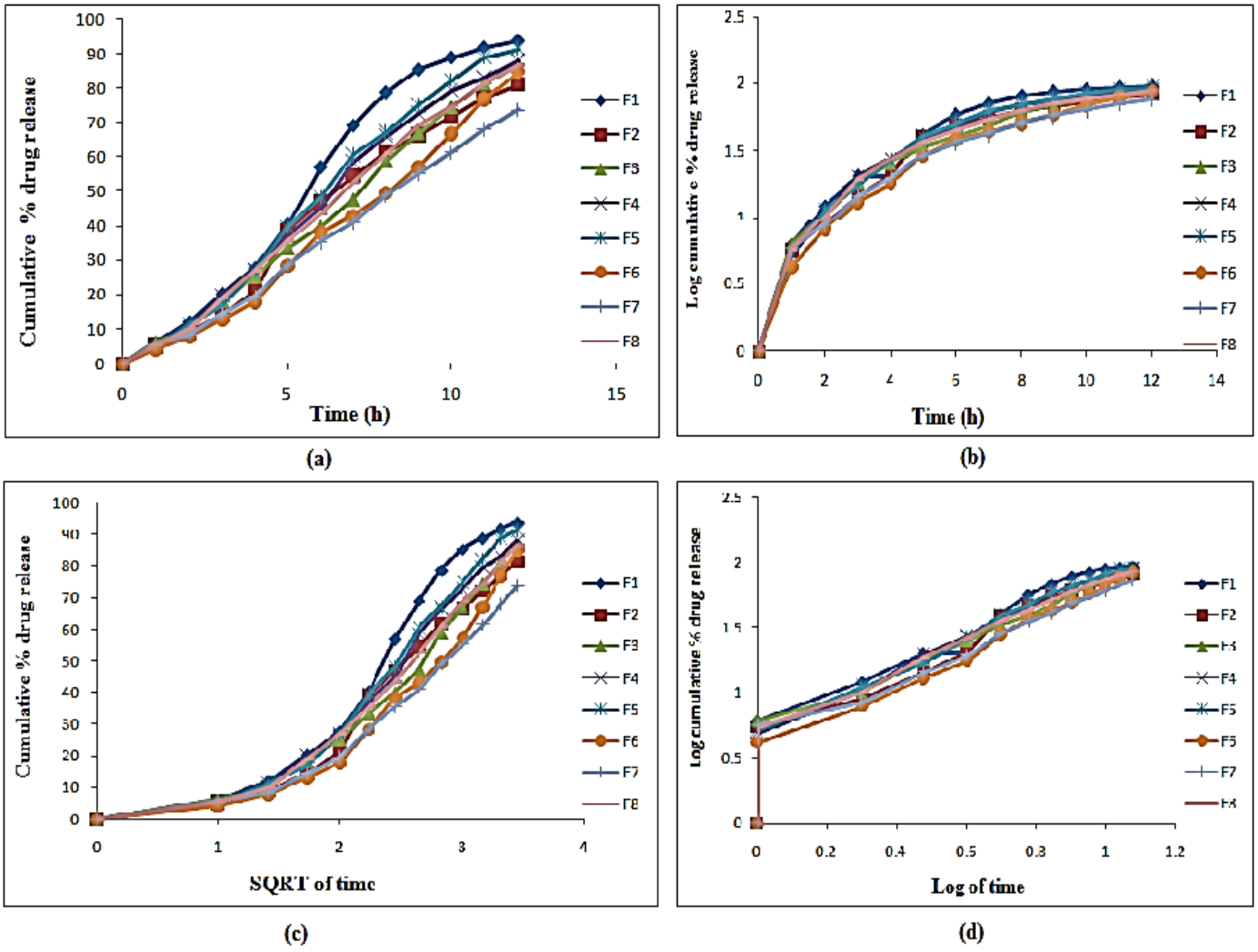

Fig 4: Release Kinetics of DCL Loaded Microspheres Fitted with (a) Zero-order Model (b) First-order Model (c) Higuchi Model (d) Korsmeyer-Peppas Model

Table 5: Release kinetics parameters of DCL loaded microspheres.

Formulation code	Zero order model		First order model		Higuchi model		Korsmeyer-peppas model	
	r^2	k_0	r^2	k_1	r^2	k_h	r^2	n
F1	0.968	8.10	0.786	- 0.076	0.901	38.03	0.900	1.502
F2	0.978	5.24	0.800	- 0.035	0.901	24.56	0.913	1.464
F3	0.995	5.52	0.800	- 0.037	0.894	25.38	0.903	1.419
F4	0.989	6.81	0.787	- 0.055	0.909	31.65	0.917	1.489
F5	0.989	7.51	0.793	- 0.061	0.904	35.24	0.917	1.499
F6	0.987	4.96	0.852	- 0.031	0.861	23.32	0.944	1.486
F7	0.995	5.39	0.817	- 0.035	0.893	24.70	0.910	1.378
F8	0.996	5.52	0..789	- 0.049	0.909	30.20	0.908	1.446

Surface morphology analysis

Scanning electron microscopy (SEM) analysis was used to analyze the shape & structure of the prepared microspheres. The morphology of prepared microspheres was studied using SEM (FEI Quanta- 200 MK2, Netherland). All the samples were coated with gold-palladium alloy under vacuum. Coated samples were then examined using SEM analyzer. It reflected the circular shape and a little bit rough and spongy surfaces shown in Fig. 5.

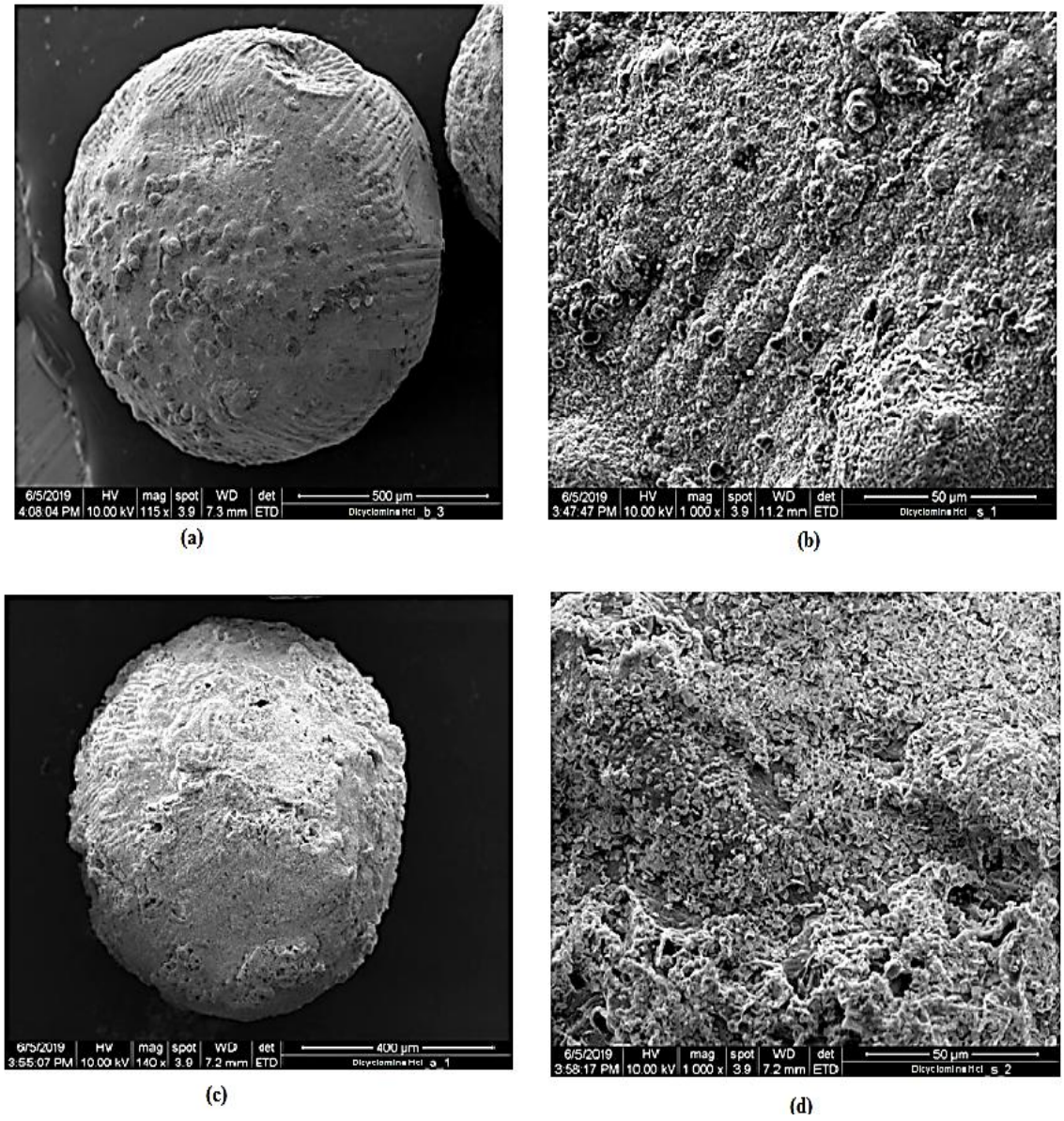

Fig 5: SEM Photograph of (a) DCL Loaded Microspheres before Dissolution (b) Surface of DCL Loaded Microspheres before Dissolution (c) DCL Loaded Microspheres after Dissolution (d) surface of DCL Loaded Microspheres after Dissolution.

Conclusion

DCL loaded guar gum-based microsphere was formulated by ionotropic gelation method using different ratio of drug-polymers. The prepared microsphere of different formulation expressed 533±0.29 µm of average particle size, 19.78 ± 0.28 of drug loading and 80.81 ±1.61 of entrapment efficiency. *In vitro* drug release study was optimized for 12 h and the release kinetics was experienced zero-order release profile

indicating a dissolution controlled system. The release pattern was also fitted with the Korsmeyer-Peppas model which was followed to case II transport system. The results of the *In-vitro* drug release indicated that developed formulations are potential formulation for targeting the dicyclomine hydrochloride to the colon. This type of polymeric formulation can also be developed to load other drugs demanding controlled release over a longer time to enhance their bioavailability and therapeutic efficacy.

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Conflict of interest
We, all the authors declare no conflict of interest.

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