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Formulation and Evaluation of Floating Natural Polymer-Based Microspheres of Doxycycline Hyclate Using Alginate-Xanthan Gum Binary System

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Abstract: Doxycycline hyclate floating microspheres were developed using a sodium alginate–xanthan gum binary matrix to provide gastroretentive sustained drug release. Nine formulations (F1–F9) were prepared by ionotropic gelation with sodium bicarbonate as the buoyancy-generating agent and calcium chloride as the cross-linker. The microspheres were evaluated for practical yield, particle size, entrapment efficiency, buoyancy, drug content, Fourier-transform infrared compatibility, and in vitro drug release. Increasing polymer concentration generally increased particle size, entrapment, and buoyancy while slowing drug release. F8 showed the most suitable overall performance, with a practical yield of 88.26 ± 6.74%, particle size of 604.52 ± 46.38 µm, entrapment efficiency of 86.28 ± 6.32%, buoyancy of 88.64 ± 6.46%, and drug content of 98.52 ± 1.12%. The formulation released 91.64% of doxycycline at 12 h. Its release behaviour was best described by the Korsmeyer–Peppas model and was reported as non-Fickian. F8 also retained acceptable characteristics during 60 days of accelerated storage. The study demonstrated the formulation feasibility of alginate–xanthan gum floating microspheres for sustained doxycycline delivery.

Keywords: Doxycycline hyclate; floating microspheres; sodium alginate; xanthan gum; ionotropic gelation; gastroretentive drug delivery; sustained release.

INTRODUCTION

Gastroretentive drug-delivery systems are intended to prolong residence of a dosage form in the stomach and can be designed as floating, mucoadhesive, expandable, high-density, magnetic, or raft-forming systems. Floating multiparticulate systems are of particular interest because they distribute the dose among numerous low-density units while providing buoyancy and controlled release. Compared with a single-unit system, floating microspheres may provide broader intragastric distribution and a lower risk of dose dumping, although their in vivo performance remains dependent on gastric physiology and formulation properties [1,2].

Natural polymers are frequently used in controlled-release formulations because of their gel-forming capacity, biodegradability, and ability to modify hydration and drug diffusion [3,4]. Sodium alginate is an anionic polysaccharide that readily forms calcium-cross-linked matrices through ionotropic

gelation and is widely used for microsphere preparation [5,6]. Xanthan gum is a hydrophilic microbial polysaccharide that increases viscosity and gel strength and can retard diffusion from hydrated matrices [7,8]. Combining alginate and xanthan gum can therefore couple efficient particle formation with improved matrix integrity and release control. A recent multiparticulate study using xanthan gum with alginate also supported the usefulness of this polymer combination for modifying entrapment and release behaviour [9].

Doxycycline hyclate is a water-soluble tetracycline antibiotic used in a range of bacterial infections. Oral doxycycline is generally well absorbed, but conventional products may be associated with nausea, gastrointestinal irritation, dysphagia, oesophagitis, and oesophageal ulceration when administration is inappropriate [10,11]. A sustained particulate system may modify the release pattern; however, because doxycycline is an antibiotic and can irritate the gastrointestinal tract, prolonged gastric exposure requires careful formulation and should not be assumed to improve clinical outcomes without in vivo evidence.

Previous formulation studies have incorporated doxycycline into alginate microparticles, PLGA microspheres, in situ gels, and chitosan-based microparticles or microspheres to obtain prolonged or localized delivery [12–17]. Floating microsphere studies with other drugs have also shown that polymer concentration and matrix composition can influence particle size, entrapment, buoyancy, and release [18]. These reports support the pharmaceutical feasibility of polymeric particulate carriers, but the combined use of sodium alginate and xanthan gum as a floating binary matrix for doxycycline hyclate requires direct formulation evaluation.

Accordingly, the present study was undertaken to formulate doxycycline hyclate floating microspheres by ionotropic gelation using sodium alginate and xanthan gum at different concentrations, with sodium bicarbonate as the floating agent and calcium chloride as the cross-linker. The formulations were compared for microsphere yield, particle size, entrapment efficiency, buoyancy, drug content, compatibility, in vitro release, and short-term accelerated stability.

MATERIALS AND METHODS

Chemicals

Doxycycline hyclate was obtained as a gift sample from Cipla Ltd., Mumbai, India. Sodium alginate was procured from HiMedia Laboratories Pvt. Ltd., Mumbai, India; xanthan gum from Merck Life Sciences, Mumbai, India; sodium bicarbonate from MG Dehydrated, Hyderabad, India; and calcium chloride from Merck Life Sciences, Mumbai, India.

Analytical and compatibility studies

A stock solution of doxycycline hyclate was prepared in pH 6.8 phosphate buffer and suitable dilutions over 2–10 µg/mL were analysed at 276 nm. Drug–excipient compatibility was examined by ATR-FTIR spectroscopy over 4000–400 cm^{-1} by comparing spectra of pure doxycycline, sodium alginate, xanthan gum, and the physical mixture.

Formulation design and preparation of floating microspheres

Nine formulations were designed by varying sodium alginate from 1.5% to 2.5% w/v and xanthan gum from 0.25% to 0.75% w/v, while doxycycline hyclate, sodium bicarbonate, and calcium chloride were kept constant. The composition is shown in Table 1.

Table 1: Composition of doxycycline hyclate floating microspheres

Formulation	Doxycycline hyclate	Sodium alginate (% w/v)	Xanthan gum (% w/v)	Sodium bicarbonate (% w/v)	Calcium chloride solution (% w/v)	Distilled water
F1	100 mg	1.5	0.25	0.5	2.0	q.s.
F2	100 mg	1.5	0.50	0.5	2.0	q.s.

F3	100 mg	1.5	0.75	0.5	2.0	q.s.
F4	100 mg	2.0	0.25	0.5	2.0	q.s.
F5	100 mg	2.0	0.50	0.5	2.0	q.s.
F6	100 mg	2.0	0.75	0.5	2.0	q.s.
F7	100 mg	2.5	0.25	0.5	2.0	q.s.
F8	100 mg	2.5	0.50	0.5	2.0	q.s.
F9	100 mg	2.5	0.75	0.5	2.0	q.s.

Sodium alginate and xanthan gum were dispersed in distilled water with continuous agitation to obtain a homogeneous polymer phase. Doxycycline hyclate was incorporated, followed by sodium bicarbonate. The drug–polymer dispersion was introduced dropwise through a syringe into stirred calcium chloride solution. After ionotropic gelation and curing, the microspheres were separated by filtration, washed with distilled water, dried, and stored in a desiccator until evaluation.

Evaluation of microspheres

The dried microspheres were evaluated for practical yield and mean particle size. Particle size was measured microscopically using a calibrated ocular micrometer, with at least 50 microspheres examined per formulation. For entrapment efficiency, 50 mg of microspheres was crushed and dispersed in 100 mL of pH 6.8 phosphate buffer, sonicated, filtered, and analysed at the doxycycline wavelength maximum. Buoyancy was assessed in 0.1 N HCl (pH 1.2) by separating, drying, and weighing floating and settled fractions. Drug content was determined by the analytical method described in the thesis.

In vitro drug release and release behaviour

In vitro dissolution was evaluated using a USP type II paddle apparatus. Microspheres equivalent to the required drug dose were placed in the dissolution medium, and samples were withdrawn at predetermined intervals and replaced with equal volumes of fresh medium. Doxycycline concentration was measured by UV–visible spectrophotometry and cumulative percentage release was calculated from the calibration relationship. Release was followed for 12 h.

Stability study

The optimized formulation was stored at 40 ± 2°C/75 ± 5% RH for 60 days in accordance with the stability approach described in the thesis and ICH Q1A(R2) [19]. Samples were assessed at 0, 30, and 60 days.

RESULTS AND DISCUSSION

Calibration of DXC

A primary DXC solution was obtained by dissolving 50 mg of drug in water and making the volume to 100 mL. A 10 mL aliquot was then placed in a 100 mL volumetric flask and diluted to volume to prepare the working standard. Further dilutions provided concentrations of 2–10 µg/mL. Absorbance was recorded at 276 nm, and the resulting calibration plot in pH 6.8 phosphate buffer was linear, with $R^2 = 0.9978$.

Drug – excipient Compatibility Studies

Drug–excipient compatibility was examined by FTIR spectroscopy. Spectra were recorded for pure DXC, sodium alginate, xanthan gum, and their physical mixtures, and the resulting profiles were compared for evidence of interaction. Retention of the principal drug bands without the appearance or disappearance of diagnostic peaks was interpreted as an absence of chemical incompatibility. The spectra were also used to

verify the presence of the API within the physical mixtures and to describe relevant changes in band position or intensity.

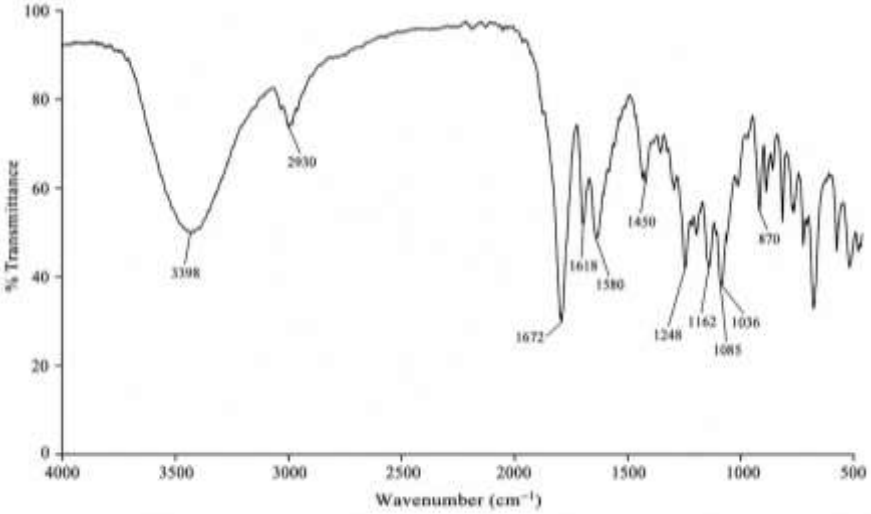

Fig 1: FTIR spectral plot of pure DXC

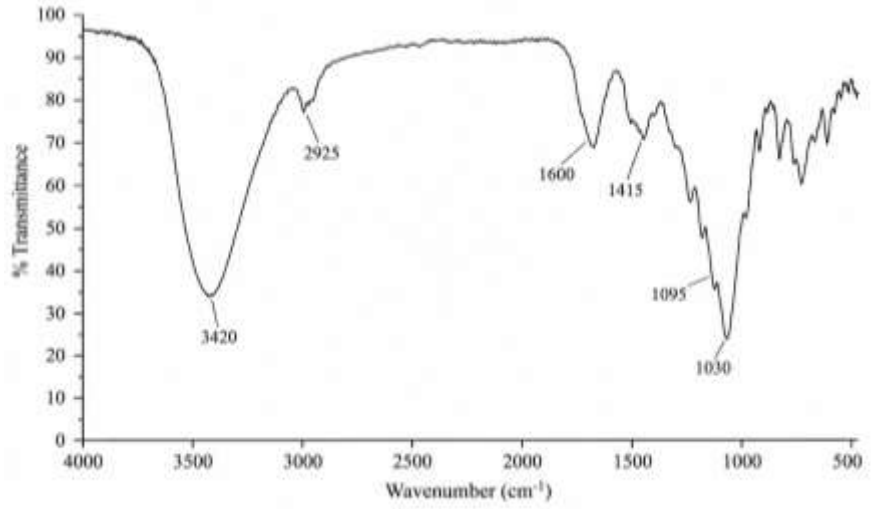

Fig 2: FTIR Spectral plot of sodium alginate

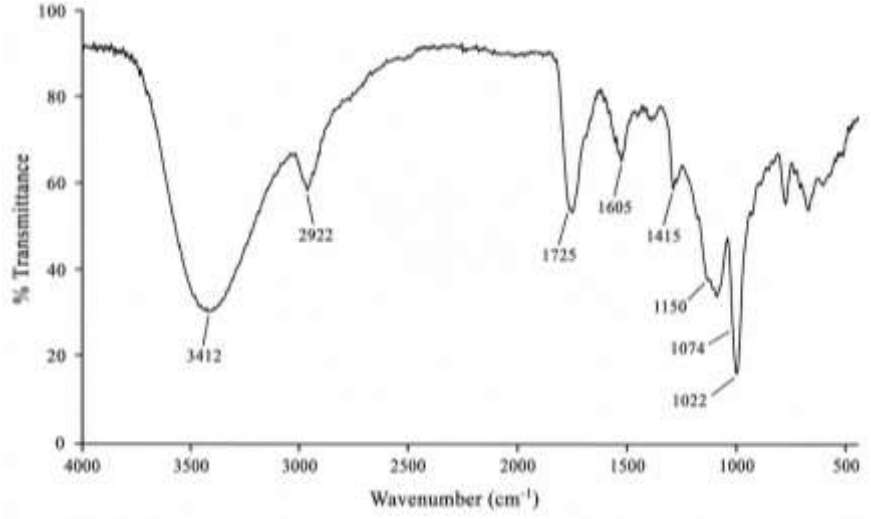

Fig 3: FTIR Spectral plot of xanthan gum

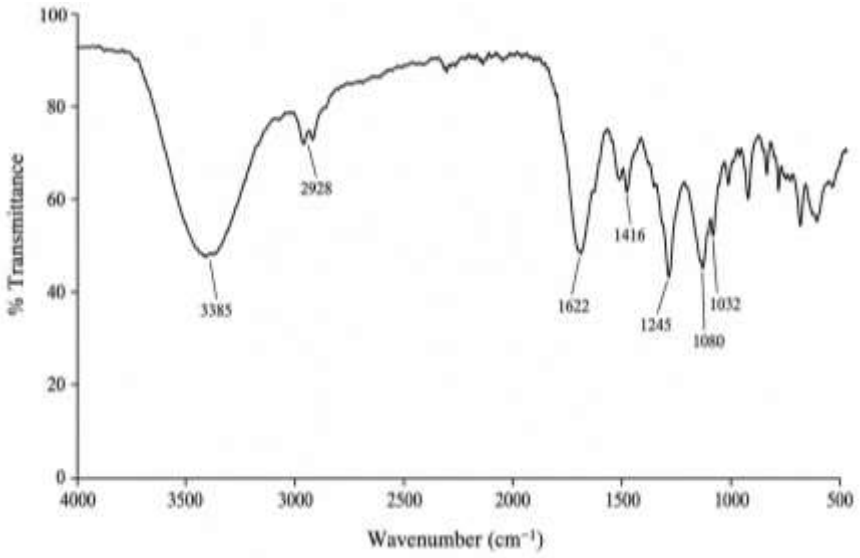

Fig 4: FTIR Spectral plot of optimized formulation

Table 2: Comparative FTIR peak assignments

Functional group	Pure doxycycline (cm^{-1})	Sodium alginate (cm^{-1})	Xanthan gum (cm^{-1})	Doxycycline + alginate + xanthan gum (cm^{-1})
O–H and N–H stretching	3398	3420	3412	3385
Aliphatic C–H stretching	2930	2925	2922	2928
Carbonyl stretching region	1672	–	1725	–
Aromatic and carboxylate region	1618, 1580	1600	1605	1622
Carboxylate and CH bending region	1450	1415	1415	1416
C–O and C–N fingerprint region	1248, 1162, 1085, 1036	1095, 1030	1150, 1074, 1022	1245, 1080, 1032
Additional fingerprint region	870	–	–	–

Microsphere characteristics

All formulations produced measurable yields with acceptable drug incorporation and buoyancy. Practical yield ranged from 72.45 ± 4.86% to 88.26 ± 6.74%, with the highest value for F8. Mean particle size increased from 412.35 ± 28.64 µm in F1 to 638.75 ± 49.24 µm in F9 as polymer concentration increased. The trend was consistent with increased feed viscosity producing larger droplets during ionotropic gelation.

Entrapment efficiency increased overall with polymer level, ranging from 68.32 ± 4.10% to 86.28 ± 6.32%. Buoyancy ranged from 70.25 ± 4.36% to 88.64 ± 6.46%, with F8 again showing the highest value. Drug content remained within 94.18 ± 1.42% to 98.52 ± 1.12%. The combined results indicate that increased polymer concentration improved matrix formation and drug retention, although the highest polymer level did not further improve all responses.

Table 3: Practical yield, particle size, entrapment efficiency, buoyancy, and drug content

Formulation	Practical yield (%)	Particle size (µm)	Entrapment efficiency (%)	Buoyancy (%)	Drug content (%)
F1	72.45 ± 4.86	412.35 ± 28.64	68.32 ± 4.10	70.25 ± 4.36	94.18 ± 1.42
F2	75.68 ± 5.12	438.72 ± 31.25	71.46 ± 4.82	73.48 ± 4.75	95.26 ± 1.38
F3	78.34 ± 5.46	467.54 ± 34.18	74.28 ± 5.06	76.52 ± 5.12	96.14 ± 1.56
F4	80.26 ± 5.74	489.63 ± 36.42	76.85 ± 5.24	78.36 ± 5.48	96.82 ± 1.31
F5	83.72 ± 6.18	518.47 ± 39.56	80.42 ± 5.78	82.64 ± 5.62	97.45 ± 1.24
F6	86.54 ± 6.42	546.28 ± 41.30	83.76 ± 6.04	85.72 ± 6.18	98.16 ± 1.18
F7	84.18 ± 6.05	572.36 ± 43.74	81.34 ± 5.96	83.45 ± 5.84	97.62 ± 1.36
F8	88.26 ± 6.74	604.52 ± 46.38	86.28 ± 6.32	88.64 ± 6.46	98.52 ± 1.12
F9	87.42 ± 6.58	638.75 ± 49.24	85.64 ± 6.24	87.26 ± 6.38	98.34 ± 1.25

In vitro drug release

All formulations showed sustained doxycycline release over 12 h. Lower-polymer formulations released the drug more rapidly, whereas higher polymer concentrations generally slowed release by increasing matrix viscosity and diffusional resistance. F1 released 99.18% at 12 h, while F9 released 76.82%. F8 released 91.64% at 12 h.

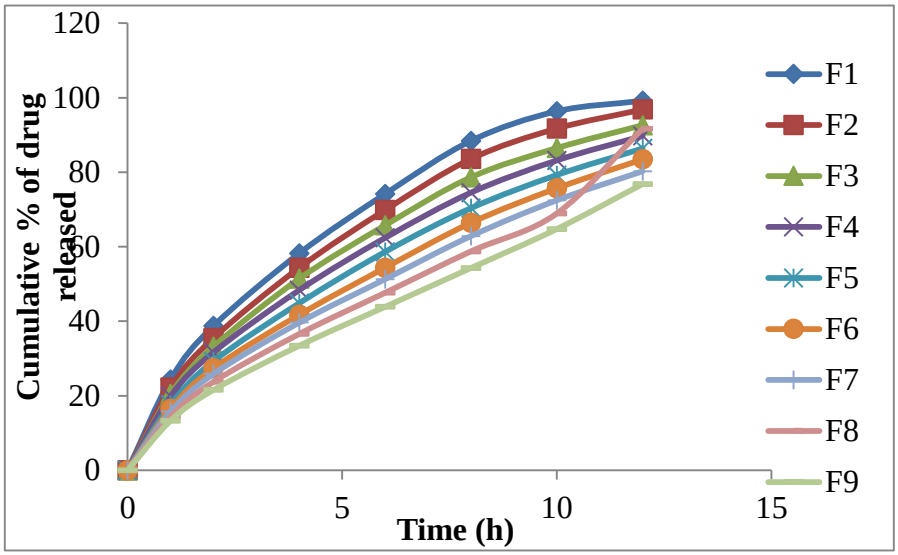

Fig 5: In-vitro dissolution profile of DXC formulations (F1-F9)

Optimized formulation, and stability

F8 was retained as the optimized formulation because it combined 88.26 ± 6.74% practical yield, 604.52 ± 46.38 µm particle size, 86.28 ± 6.32% entrapment efficiency, 88.64 ± 6.46% buoyancy, 98.52 ± 1.12% drug content, and 91.64% release at 12 h.

During 60 days of accelerated storage, F8 remained light yellow and free-flowing with no reported physical deterioration. At 60 days, drug content was 96.94%, entrapment efficiency 84.96%, buoyancy 86.84%, and 12 h drug release 89.72%. The modest changes indicated acceptable short-term stability under the tested conditions.

CONCLUSION

Floating microspheres of doxycycline hyclate were successfully prepared by ionotropic gelation using a binary sodium alginate–xanthan gum matrix. Variation in polymer concentration influenced particle size, yield, entrapment efficiency, buoyancy, drug content, and the rate of drug release. Higher polymer levels generally increased particle size and matrix retention while reducing the release rate. Among the nine formulations, F8 provided the most appropriate overall balance, with high practical yield, entrapment efficiency, buoyancy, drug content, and sustained release over 12 h. FTIR findings suggested the absence of a major chemical incompatibility between doxycycline and the selected polymers. The release behaviour was reported to follow the Korsmeyer–Peppas model with non-Fickian transport, and F8 retained acceptable characteristics during 60 days of accelerated storage. The results establish the pharmaceutical feasibility of the alginate–xanthan gum microsphere system.

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