Formulation &invitro evaluation of clarithromycin floating microsponge capsule

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ABSTRACT:

Objective: The aim of this study is to formulate microsponge of clarithromycin capsule dosage form and evaluate the release profile in comparing with marketed clarithromycin (Clamycin)

Methods: clarithromycin microsponge was prepared by quasi-emulsion solvent diffusion method by using polymers Eudragite RL100 in organic solution as internal phase and aqueous solution of polyvinyl alcohol as external phase. The compatibility of the drug with formulated components was established by Fourier Transform Infra-Red (FTIR) spectroscopy. The prepared microsponge powder was evaluated for angle of repose, Carr's Index ,particle size, floating time production yield, drug loading efficiency of microsponges and release profile in comparison with marketed drug.

Results: Formulation F4 with a ratio 8:1 drug to polymer, and 0.25% polyvinyl pyrrolodine solution was the best formulation showing the highest degree of sustained release that was 79.59% at the end of 12 hours with a floating time capsule 12 hr. Eudragit RL 100 could control drug release in stomach.

تحضير وتقيم كبسول الكلارثرومايسين المايكرو اسفنجي العائم

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مفتاح الكلمات: المايكرو □فنجي، كلارثرومايسين، طريقة انتشار المذيبات الشبه مستحلبه

الخلاصة:

ان الهدف من هذا الدرا□ه هو □ياغه الكلارثرومايسن المايكرو □فنجي العائم كشكل من اشكال الجرع الدوائيه وهو الكبسول وتقيم التحرر الدوائي له ومقارنته مع دواء الكلاميسين المتوفر في السوق . تم تحضير العديد من □يغ الكلارثرومايسين المايكرو□فنجي بطريقه انتشار المذيب في شبه المستحلب بوا□طة □تعمال اليودراجيت بوليمر(RL100) المبطئ للتحرر في المحلول العضوي كو□ط داخلي ومحلول مائي من البوليفنيل الكحول كو□ط خارجي. تم تقييم التركيبات لخصائص التدفق،الطفو, □جم الجزيئات وتحرر الماده الفعاله و توافق الدواء مع باقي مكونات التركيبة بوا□طه FTIR .

اظهرت النتائج ان افضل □يغه هي F4 التي□ضرت بتركيز نسبه الدواء الى البوليمر 1:8 ومثبت بتركيز 0.25 كما اظهرت أفضل تدفق وطوفان لكلارثرومايسين المايكرو □فنجي لمده 12□اعة.

1. INTRODUCTION:

Clarithromycin (CLR) is a macrolide antibiotic with a broad spectrum of activity. It is be given for treatment of respiratory tract infections and skin and soft tissue infections.

CLR may be given to eradicate *H. pylori* for treatment regimens of peptic ulcer diseases. [1] CLR is rapidly absorbed from the gastrointestinal tract and undergoes first pass metabolism. The bioavailability of the drug is about 55%. It is be given in a dose of 250 mg or 500 mg as tablets or suspension dosage forms. The terminal half-life of CLR is reportedly about 3-4 hours. Thus, CLR has all the requisites of gastro retentive drug delivery system. [2]

Eudragit polymers have an ability to resist the acid environment of stomach and retain there for prolonged period. [3]

Hence, an attempt was be made to develop floating micros- pong of CLR using eudragit polymers with an aim to retain the microsponges in the stomach for prolonged period.

Microsponges are highly cross linked patented, porous, polymeric microspheres that acquire the flexibility to entrap a wide variety of active ingredients that are mostly used for prolonged topical administration and recently for oral administration. They are tiny, sponge like spherical particles that consist of a myriad of interconnecting voids within a non-collapsible structure with a large porous surface. Moreover, they enhance stability, reduce side effects and modify drug release. [4]

2. MATERIALS AND METHODS

Materials:

Clarithromycin (gifted by Samarra Drug Industries (SDI), Iraq), Evonik Degussa Ltd., India provided Eudragit RL 100 as gift sample. Clamycin ® provided by julphar company, All other chemicals used were of analytical grade.

Methods

Clarithromycin floating microsponges were prepared by quasi- emulsion solvent diffusion method. The internal phase was eudragit RS-100 dissolved in 10 ml mixture of dichloromethane and ethanol (1:1) at room temperature. This was, followed by addition of drug with sonication for 15min. The internal phase was then poured into polyvinyl alcohol (PVA) solution in water, the external phase with stirring, and the microsponges then washed and filtered, then dried at 40°C for 12 hours.

The composition of the prepared formulations are shown in table (1).

Table1: Composition of all the formulations (Batch F1 – Batch F7)

Formulation cod	Drug: polymer ratio	ethanol:dichloro-methane volume	PVA (%w/v)	**Water(ml)**
F1	1:1	10	0.25	**200**
F2	2:1	10	0.25	**200**
F3	4:1	10	0.25	**200**
F4	8:1	10	0.25	**200**
F5	12:1	10	0.25	**200**
F6	2:1	10	0.5	**200**
F7	2:1	10	0.75	**200**

Microsponge Characterization:

Particle size analysis.

The particle size and size distribution of the prepared microsponges were determined by using optical microscopy method .approximately 200- 300 microsponge were counted for particle size using a calibrated optical microscope (Olympus Pvt. Ltd., India) .[5]

Drug-excipients compatibility studies

Fourier transform infrared (FTIR) spectroscopic

Drug-excipient interaction is one of the most important compatibility studies, FTIR study used for this purpose on samples of pure clarithromycin and the blend powder of selected formula. Spectra obtained by using (Shimadzu 8300, Japan) according to KBr disk method. About 2-3 mg sample were mixed with dried IR grade potassium bromide powder and the spectra were in between the wave number range of 4000-400 cm^{-1}

Production yield and loading efficiency

Asample of microsponge which equivalent to 100 mg of CLR was dissolve in 100 ml of 0.1 N HCL. The absorbance was measured spectrophotometriclly at 275 nm. Then Percentage yield can calculated using the equation (1) as following :

Production yield (PY) = (Final obtained mass of microsponge / initial mass of polymer and drug) × 100. ---------eq. (1)

The drug loading efficiency of the microsponge can be computed using equation (2) as following:

Loading Efficiency (LE %) = (Actual drug content / Theoretical drug content) × 100 --- eq. (2). [6]

Determination the flowability of powder

A. Bulk density and tapped density.

Both loose bulk density (LBD) and Tapped bulk density were determined. Powder of microsponge was taken in a 10ml measuring cylinder and initial volume was write and tapped at height of 2.5cm at 2-second intervals until no further change in volume was noted after tapping.

LBD and TBD calculated using the following formula.

LBD = Weight of the powder/volume of the packing

TBD= Weight of the powder/Tapped volume of the packing. [7]

B. Determination of carr's index:

The compressibility index of the powder determined by the Carr's Compressibility index as shown in equation (3)

Carr's index (%) = (TBD-LBD) x100/TBD. --------- eq. (3). [8]

C. Determination of the angle of repose

Angle of repose was measured for the microsponge powder, to observe the flow properties of powders. The Funnel method was used; the powder was allowed to pass freely through a funnel and poured onto a horizontal plane, fixed base diameter, free of vibration petri dish to form a cone. The funnel height was maintained at approximately 2-4 cm from the tip of the powder pile in order to minimize the impact of the falling powder on the tip of the cone.

The tan of angle of repose (θ) was calculated after measuring the height (H) of the cone of the powder utilizing equation no. (4):

$\tan \Theta = h/r$ … equation (4)

The accepted limit of good flow properties is (20-30). [9]

Optimization of formulation parameters and process factors:

The effect of drug: polymer ratio, concentration of emulsifying agent and volume of solvent was determined and show effect on particle size, production yield and drug loading efficiency

In vitro buoyancy study:

Buoyancy test was determined by using USP type II apparatus at 50 rpm maintained at 37±0.5°C. The capsules were be placed in 900 ml jar containing 0.1N HCl as dissolution medium. The time required the capsule to rise to the surface and float was determined as floating lag time, while the time during which the capsules remained buoyant was the floating time. [10]

In vitro dissolution studies:

The release rate of CLR from floating microsponge capsules (n=3) was determined using USP dissolution test apparatus Type II (paddle method). The dissolution test was carried out by using 900 ml of 0.1NHCl at 50 rpm. The temperature of the medium maintained at 37±0.5ºC and the study carried out for 12 hrs. Samples of 5 ml were be withdrawn at an interval of every hour; the withdrawn samples were replaced with fresh dissolution medium. The samples filtered through Whatman filter paper, and then analyzed spectrophotometrically at 275 nm. [11]

3. RESULTS AND DISCUSSION:

Evaluation of clarithromycin microsponge formulation:

The clarithromycin floating microsponge was prepared by quasi-emulsion solvent diffusion method. This method found to be very easy, reproducible, rapid and avoid solvent toxicity. [12]

The microsponges found to be uniform in size**.** Particle size of prepared microsponges was in the range of 78.3 ± 12.5 µm to 39.4 ± 12.5µm (Table 2**)** the sizes of microsponges affect the encapsulation efficiency and the release rate of the drug. It observed that as the ratio of drug to polymer was increased, the particle size decreased. This could probably be due to the fact that in high drug to polymer ratio, the amount of polymer available per microsponge was comparatively less. Probably in high drug-polymer ratios, less polymer amounts surround the drug were obtained which reduce the thickness of polymer wall and microsponges with smaller size. [13]

The effect of concentration of PVA on size of microsponges was studies for optimized formulation. The selected concentration of PVA was 0.25% (F2) since 0.5 % of PVA (F6) the particle size increased from 60.3 ± 10.3 µm to77 ± 12.5 µm. Further increasing the concentration to 0.75 % of PVA (F7) the particle size increased to 83.3± 15 µm.

The dispersion of the solution of the drug and polymer into droplets affected by the concentration of PVA in the external phase. When the concentration of PVA increased, the size of microsponges increased which may be explained to be due to the increased viscosity wherein larger emulsion droplets formed resulting in larger microsponges.[14]

Fourier transform infrared (FTIR)

Fourier transform infrared (FTIR) spectral study was done to find out the chemical stability or interaction of the excipients. In FTIR studies, the prominent peaks in the FTIR spectrum of pure drug CLR (figure1) at 1730.18 for O-C=O stretching vibration in a lactone ring, characteristic peaks of C=O stretching vibration from ketone group in a lactone ring at 1691.03 cm−1 , 3468.85 for Tertiary –N stretching, which are the same as the reported one. Hence, it can be concluded that there was no interaction between drug and excipients, since similar peaks of specific functional groups were be obtained as shown in figure (2). [1

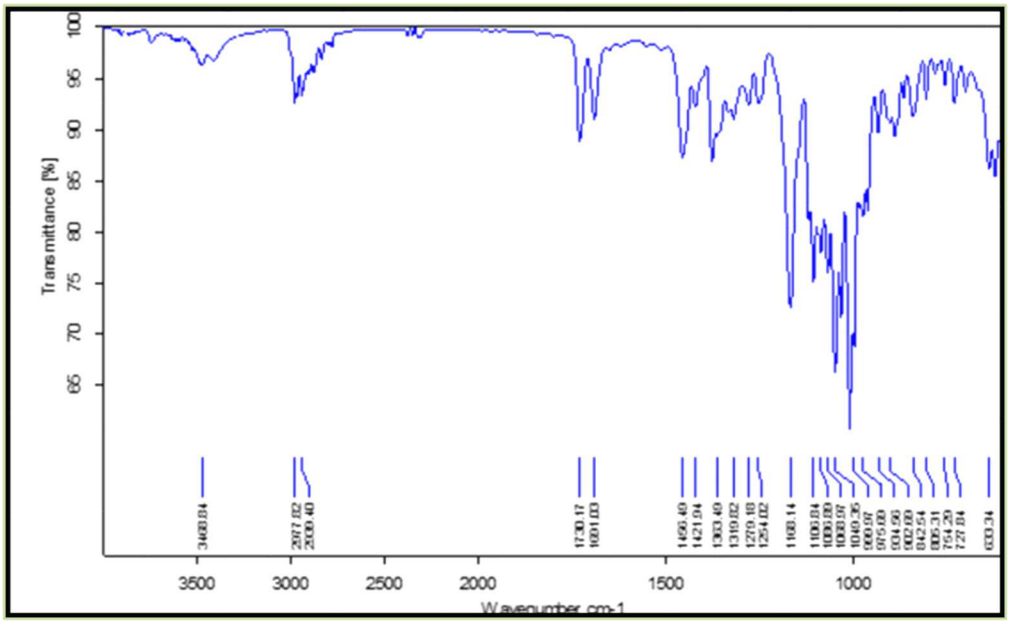

Fig. 1: FTIR spectrum of pure clarithromycin

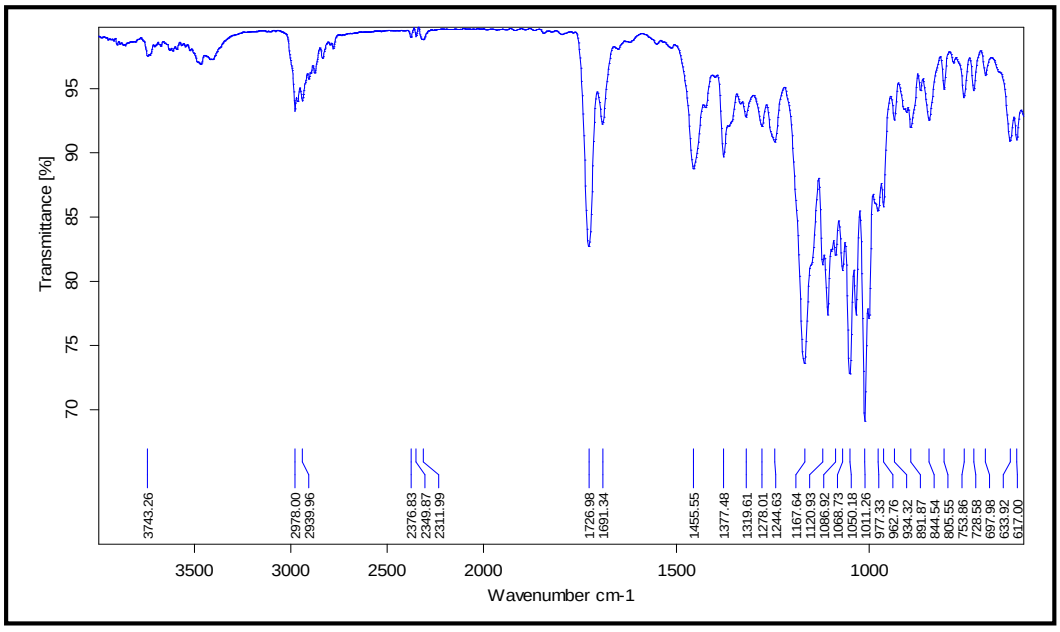

Fig. 2: FTIR spectrum of clarithromycin microsponge

Production yield:

The production yield of the prepared microsponges of clarithromycin was in the range of (53 % to 90.1 %). The loss of product may be due to the formation of some agglomerates and polymer adherence to the container because of viscous nature of slurry.[16]

Drug loading efficiency:

Drug content in different formulations estimated by UV spectrophotometric method. Loading of the drug depends on the successful molecular association of the drug with the polymers. The drug loading efficiency of the microsponges found in the range of (37% to 91.1 %). The best drug encapsulation efficiency found for the formulation F4 and F5 with the drug polymer ratio of 8:1 and 12:1 respectively. [17]

Table 2: production yield, particle size and drug loading efficiency of Prepared micros pong.

Formulation code	Production Yield (%)	Particle size (μm)	Drug loading efficiency (%)
F1	53	78.3	37
F2	68.5	69	64.2
F3	74	58	73.4
F4	88.2	50.2	90.3
F5	90.1	39.4	91.1

Determination of the angle of repose:

The results of angle of repose were shown in table (3) .the angle of repose were ranged between 25.10 ±1.12 to 24.10 ± 2.12, which indicates good flow properties of powder. [18]

Determination of carr's index:

The result of the carr's index are show in table (3), its indicted that the carr's index of all the formulation were less than 20 from (14.347 ±0.25 to 12.90±0.12) which indicate good flow properties and good compressibility.[19]

In vitro buoyancy study:

The in vitro floating test showed that the floating lag time observed in case of all formulation was zero. After placing of the CLR capsules in 0.1N HCl acid, the capsules did not reach even in the bulk of the floating medium and they showed to remain at the surface. The capsules also showed a total floating time greater than 12 hours. These results exhibited satisfactory floatable ability because of their low density and internal voids. [20]

Table 3: Bulk density, tapped density, angle of repose and carr's index % of batches (f1 –f5).

Formlua no.	Bulk density	Tapped density	Angle of repose	Carr's index %	Flow character
FI	0.462± 0.006	0.528 ± 0.008	24.02± 1.72	14.347± 0.25	**Good**
F2	0.472±0.0065	0.571±0.0102	25.34±1.15	12.32±0.99	**Good**
F3	0.512±0.007	0.527±0.0144	26.60±2.02	13.723±0.13	**Good**
F4	0.463±o.0113	0.583±0.0109	24.64±1.15	12.32±0.87	**Good**
F5	0.430±0.0061	0.517±0.0086	24.10±2.12	12.90±2.12	**Good**

In-vitro drug release studies:

In-vitro drug release studies were carried out in 0.1N HCl for 12 hours. The release profiles obtained for the formulation (F4, F5 and marketed clarithromycin) shown in Figure (3). It was observed that the drug release increases with increase in drug polymer ratio. This may be due to the fact the polymer concentration was be kept constant for each formulation while the concentration of drug molecules was increasing which results in reduced thickness of polymer coat surrounding micro particles.

The in-vitro performance of CLR floating microsponge (F5) showed prolonged and controlled release of CLR in predictable manner as the polymer concentration increases the drug release from the floating microsponge decreases. This may be explained to be due to the less water permeability of eudragit RL100 and increase in polymer thickness

will increase in diffusion and erosion pathways. Also it observed that there was insignificant differences between marketed CLR (Clamycin ®) release and the other two formulas (P<0.05) [21]

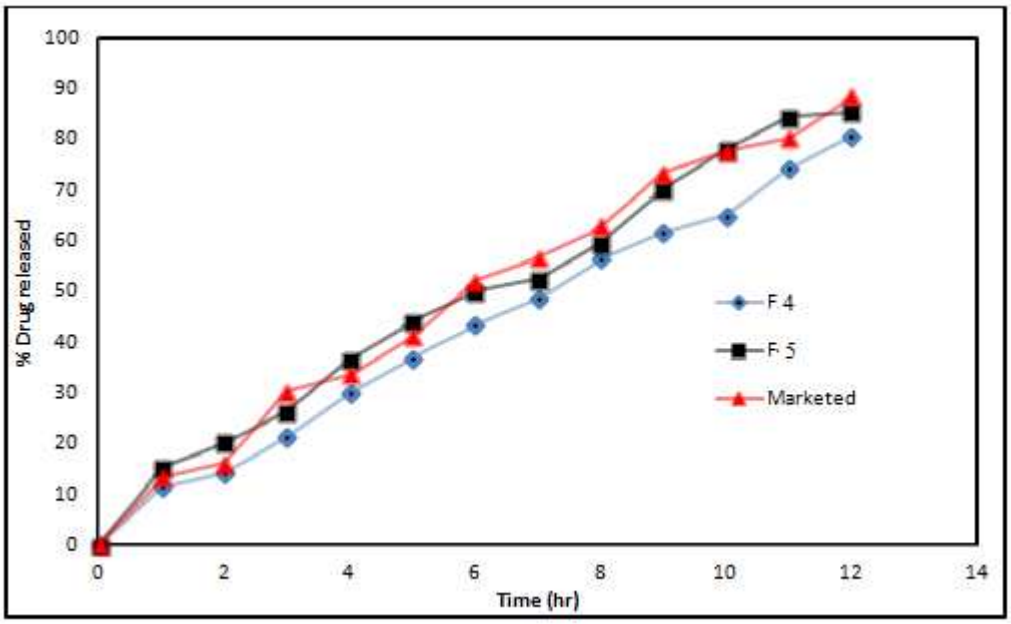

Fig. 3: The dissolution profile of formulas (F4, F5 and marketed drug (Clamycin ®))at 37ºC ± 0.5 ºC in 0.1N HCl.

CONCLUSION:

Floating microsponges of clarithromycin successfully prepared by quasi-emulsion solvent diffusion method using eudragit RL100. As the drug to polymer ratio was increased, the percentage yield of clarithromycin floating microsponge was also increased. The average particle size of clarithromycin floating microsponge has decreased with an increase in its drug to polymer ratio.Buoyancy time more than 12 hr. Microsponge containing eudragit RL100 in the ratio of 8:1 show high drug loading efficiency with particle size 50.2 µm. In-vitro release studies showed that microsponges containing eudragit RL100 in formulation F4 showed a good degree of sustained release. As the polymer, concentration increases the amount of drug-released decreases.

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