FORMULATION AND EVALUATION OF CONTROLLED DELIVERY FLOATING MICROSPHERES OF RANITIDINE HYDROCHLORIDE

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ABSTRACT

Aim: the objective of the present paper was to design and formulate Ranitidine hydrochloride (RH) floating microspheres by the emulsion solvent evaporation technique using different polymers: [Ethyl cellulose (EC) and Eudragit E100 (E E100)] with different drug: polymer ratio and at different speeds of rotation.

Methodology: the emulsion solvent- evaporation technique was used for the preparation of Ranitidine floating microspheres. The prepared microspheres were examined for their production yield, entrapment efficiency, micromeritic properties, in- vitro buoyancy and in-vitro drug release.

Results and discussion: Evaluation of micromeretics properties of the prepared microspheres showed that all formulae have good flow properties. The production yield of the microspheres ranging from 60.7% to 98.7% [the best one was (RH-EC/E E100 (1:2.5)400 rpm)] and encapsulation efficiencies ranging from 47.5% to 79.7% [the best one was (RH-EC (1:4)400 rpm)].Microspheres showed excellent buoyancy ranging from72% to 92% over 12hr [the best one was (RH-E E100 (1:1)400 rpm)] as RH microspheres with low density showed excellent floatation behavior than others with high density. In vitro release of the drug showing a biphasic pattern with controlled release during 12 hours. The release of RH increased as the concentration of polymer decreased. By combining the production yield, micromeretics parameters, entrapment efficiency and the in vitro release of RH from capsules, it was found that RH-EC/E E100 (1:2.5) 400 rpm was superior to all of the prepared formulae.

Key words: RH (Ranitidine hydrochloride), EC (Ethyl cellulose) and E E100 (Eudragite E100).

INTRODUCTION

Drug absorption from oral controlled release (CR) dosage forms is often limited by the short gastrointestinal retention time, available for absorption. Floating drug delivery systems are among the several approaches that have been developed in order to increase the gastric residence time of the dosage forms **Singh *et al.*, (2011)** .The multiple unit system has been developed to identify the merit over a single unit dosage form because the single unit. Floating systems are more popular but have a disadvantage of their "all or none" emptying process because of high variability of the gastrointestinal transit time. The synthetic polymer has been used to prepare floating microspheres. The present study was based on floating microspheres of both hydrophilic and acrylic polymers using Ranitidine hydrochloride (RH) as a model drug. It is an anti ulcer drug that has been widely used in treating gastric and duodenal ulceration and also in Zollinger Ellison syndrome. It is poorly absorbed from the lower GIT and has a short elimination half life of 2-3 hours and a bioavailability of 50% **Mastiholimath *et al.*, (2008)**.

One the other hand, **EC** the ethyl ether of cellulose, is a long chain polymer of anhydroglucose units joined together by acetal linkages. It is generally considered a non-toxic, biocompatible as well as non-biodegradable polymer. These characteristics are the reasons for its extensive use in the development of oral dosage forms, especially sustained release formulations, including oral multi-unit dosage forms (i.e., microparticles) **Rowe *et al.*, (2003).**whereas**, E E100** the hydrophobic polymer which prolongs the release of water-soluble and water insoluble drugs from its matrices.

Ranitidine hydrochloride is an H2 receptor antagonist, with a short half-life and a low oral bioavailability of 50%, was selected as a model drug to formulate a controlled release formulation with improved oral bioavailability, by prolonging the gastric residence time.

The Emulsion-Solvent Evaporation method has been widely used and several modifications of it have been successfully employed for the encapsulation of drugs for that purpose.

EXPERIMENTAL PART

Materials

Ranitidine hydrochloride (RH), kindly donated by Medical Union Pharmaceuticals, Abu-Sultan, Ismailia, Egypt); Ethyl cellulose (EC) (BIO BASIC INC, Markham, Ontario-3R1G6, Canada); Eudragit E 100(E E100) (Rohm Pharma GMBH 50.277 1-243 Germany); N-Hexane, Acetone, Heavy liquid paraffin, Hydrochloric acid (pure lab. Chemicals, USA, El-Nasr chemical company, Cairo, Egypt); Sorbitan Monooleate (Span 80), Cuangdong Uanghua Chemical Co., India. All other chemicals were analytical reagent grades.

Equipment

Shimadzu double beam UV- visible spectrophotometer model (2401/PC), (Japan); Dissolution Tester, six-cup model, Erweka Apparatebau GmbH,(Germany); Magnetic stirrer with hot plate (Brandstead /Thermolyne, 50/60HZ, 220-240 volts, Dubuque /Iowa 52001 U.S.A); Electric balance, SARTORIUS AG, (Germany); Oven, Binder GmbH Bergstr. 14 D-78532 Tuttlingen / Germany; pH meter, JENWAY Designed and manufactured in the EU by Barloworld Scientific Ltd, Dunnlow, Essex, CM6 3LB (England); Shimadzu 435 U-O4 IR spectrometer, (Japan) and Differential scanning calorimeter Shimadzu DSC-50, (Japan).

Methodology

1-Preparation of Microspheres

RH Microspheres were prepared by the emulsion–solvent evaporation technique .The external phase was prepared by addition of (1%) Span 80 in heavy liquid paraffin. The polymers used (EC or E E100) were dissolved in acetone until clear solution was obtained. The required amount of the drug was then added to obtain the internal phase. The external phase was mixed with the internal phase to carry out the emulsification process. Acetone was allowed to evaporate by continuous stirring at different speeds and then at room temperature using magnetic stirrer. Stirring was continued at room temperature until complete evaporation of the solvent, (about 5 hours). Liquid paraffin was decanted and the microspheres produced were filtered off, washed three times with n-hexane (3× 50 ml) to remove the remaining oily phase and then dried over night at room temperature (25°C).

Optimization of microspheres formulation using factorial design (Box-Behnken design**)** based on the preliminary trials, optimization was carried out by the 3 level factorial design to produce the desirable effective percent drug entrapment and a sustained drug release pattern over 12 hours .The optimization of the floating microspheres was carried out by taking into consideration the type of polymer used , the amount of polymer and the stirring rate (RPM) as formulation variables and the percentage drug entrapment and the in vitro drug release at different times(2hr-6hr-12hr) as responses. The relationship between the

process variables and the responses were evaluated by the 3 level full factorial design and response surface methodology **(Brijesh *et al.*, 2004; Jayavadhan *et al.*, 2010)**

The suggested formulae of Ranitidine hydrochloride were tabulated in Table (1).

2-Determination of the production yield of RH microspheres

The production yield which a measure of the actual weight of the prepared microspheres (drug + polymer + any other additives). This value was calculated by dividing the actual weight of the prepared RH microspheres by the theoretical weight. Thus, the dried microspheres were weighted to determine the production yield (%) of the recovered microspheres using the equation: **(El-Kamel *et al.*, 2006).**

$$\text{Yield \%} = \frac{\text{Weight of the collected microspheres}}{\text{Total weight of drug and polymer used}} \times 100$$

3-Determination of the entrapment efficiency in the prepared microspheres

The entrapment efficiency of RH microspheres was determined in 0.1 N HCl by the following method:

A weighed quantity of microspheres equivalent to 100mg of the pure drug was taken in 100ml volumetric flask and dissolved in 0.1 N HCl using sonication for 5min and the volume was made up to 100ml with 0.1 N HCl. The solution was then filtered through (0.45 µm membrane filter). The absorbance was measured after suitable dilutions with 0.1 N HCl solutions at 312.6 nm by using 0.1N HCl as blank. All analyses were carried out in triplicates

4-Micromeritic properties of the prepared RH microspheres

The prepared microspheres were evaluated through determination of the following parameters:

a- Densities of microspheres

Both loose bulk density (D_b) and tapped bulk density (D_t) were determined. A quantity of 10g microspheres from each batch was introduced into a 10 ml measuring cylinder. The initial volume was observed, and then the cylinder was allowed to stroke. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas (**Tayade and Kale, 2004**):

$$D_b = \text{Wt/ bulk volume} = W/V_b$$

$$D_t = \text{Wt/ tapped volume} = W/V_t$$

b- Hausner Ratio

It is the ratio between bulk density and tapped density. It gives an idea about the flow characters of powder particles **(Kumar *et al.*, 2002).**

$$\text{Hausner ratio} = D_t / D_b$$

c- Compressibility percent (Car's Index)

Compressibility is indirectly related to the relative flow rate, cohesiveness, and particle size of a powder. The compressibility percent of a material can be estimated as **(Staniforth, 2002)** :

$$\text{Compressibility \%} = (D_t - D_b / D_t) \times 100$$

d- Angle of Repose

It was measured by passing the microspheres through a funnel which was maintained at a fixed height in all experiments. The height (h) and radius (r) of the cone were determined. The angle of repose is calculated from the equation **(Sajeev *et al.*, 2002; Shariff *et al.*, 2007).**

$$\tan \Theta = h/r$$

5-In-vitro buoyancy of RH microspheres

The floating microspheres (100 mg) were spread over the surface of the dissolution medium (simulated gastric fluid, SGF, pH (1.2) that was agitated by a paddle rotating at 100

rpm. After agitation for the predetermined time interval, the microspheres floating over the surface of the medium and those settled at the bottom of the flask were recovered separately, deried, weighed and their buoyancy was calculated by the following equation **Singh *et al.*, 2011**)

Buoyancy (%) = $Q_f / (Q_f + Q_s)$

Where Q_f and Q_s are the weight of the floating and the settled microspheres respectively

6-In-vitro Release Study

The in-vitro release of RH from the prepared microspheres as well as from hard gelatin capsules filled with known amount of microspheres (equivalent to 100 mg of RH) was carried out at 37 ± 0.5 °C for 12 hours, using apparatus II.The baskets were rotated at 100rpm. The dissolution medium was 900 ml 0.1 N HCl pH 1.2. 5 ml samples were withdrawn replaced with fresh medium at each appropriate time intervals. The drug content in the filtered samples was measured spectrophotometrically at 312.6 nm **(Singh *et al.*, 2011)** after suitable dilutions. The release experiments were repeated in triplicates.

Table (1): Composition of Different Suggested Formulae of Ranitidine Hydrochloride Microspheres Using Ethyl cellulose and Eudragit E100

Formula No.	RH (mg)	Mg St (mg)	EC (mg)	E E100 (mg)	Span 80	D:P Ratio	Speed (rpm)
RH - EC (1:2.5) 300 rpm	500	500	1250	-	1%	1:2.5	300
RH - EC/E E 100 (1:2.5) 400 rpm	500	500	625	625	1%	1:2.5	400
RH - EC/E E 100 (1:2.5) 400 rpm	500	500	625	625	1%	1:2.5	400
RH - EC (1:1) 400 rpm	500	500	500	-	1%	1:1	400
RH - E E 100 (1:1) 400 rpm	500	500	-	500	1%	1:1	400
RH - E E 100 (1:2.5) 500 rpm	500	500	-	1250	1%	1:2.5	500
RH - EC/E E100 (1:4) 500 rpm	500	500	1000	1000	1%	1:4	500
RH - EC/E E100 (1:1) 300 rpm	500	500	250	250	1%	1:1	300
RH - E E 100 (1:4) 400 rpm	500	500	-	2000	1%	1:4	400
RH - E E 100 (1:2.5) 300 rpm	500	500	-	1250	1%	1:2.5	300
RH - EC/E E100 (1:1) 500 rpm	500	500	250	250	1%	1:1	500
RH - EC/E E100 (1:4) 300 rpm	500	500	1000	1000	1%	1:4	300
RH - EC (1:4) 400 rpm	500	500	2000	-	1%	1:4	400
RH - EC/EE 100 (1:2.5) 400 rpm	500	500	625	625	1%	1:2.5	400
RH - EC (1:2.5) 500 rpm	500	500	1250	-	1%	1:2.5	500

RESULTS AND DISCUSSION

The wave length of maximum absorbance of RH in 0.1 N HCl was found to be 312.6 nm. The calibration curve of RH obeyed Beer's Lambert law.

Production yield of RH microspheres

The range of the production yield of the prepared RH microspheres found to be between 60.66% and 98.68% as shown in table (2).The highest value appeared in the formula R H - EC/E E 100 (1:2.5) 400 rpm (98.68%) while the lowest value appeared in formula R H - E E 100 (1:1) 400 rpm (60.66%).

Consequently, the RH microspheres can be arranged in descending order concerning their production yield above 90 % as follows: RH - EC/E E 100 (1:2.5) 400 rpm> RH - EC/E E100 (1:4) 500 rpm >RH - EC/E E100 (1:4) 300 rpm >RH - EC (1:2.5) 500 rpm >RH - E E 100 (1:2.5) 300 rpm.

Singh *et al.*, (2011) found that the percentage of yield of RH microspheres was in range of 82.88% to 88.45% and was found to be increased by decreasing E E100 concentration. While, **Mastiholimath *et al.*, (2007)** found that the percentage of yield of RH/EC microspheres was in range of 82% to 89.31%

Entrapment efficiency of RH microspheres

Depending upon the drug to polymer ratio, the drug entrapment was found in the range of 47.5%to 79.3% as shown in table (2). The drug loading was found to decrease with increase in polymer concentration due to its higher viscosity which affects the diffusion coefficient of drug.

Punithe *et al.*, (2010) formulated floating microspheres of RH with E E100 of ratio 1:1 to1:3 and found that the entrapment efficiency was in the range 37.58+0.76 to75.79 +1.56

Kumar *et al.*, (2012) formulated floating microspheres of RH with EC of ratio 1:1 to1:5 and found the entrapment efficiency to be in the range 69.68+1.53 to73.78+3.05

The polymer ratio, polymer type and speed of rotation had variable effects on the entrapment efficiency of RH microspheres as shown in figures (1-4)

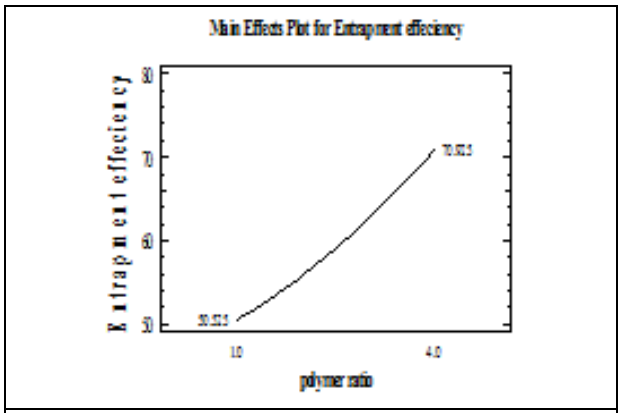

Figure (1): Effect of polymer ratio in entrapment efficiency of RH microspheres

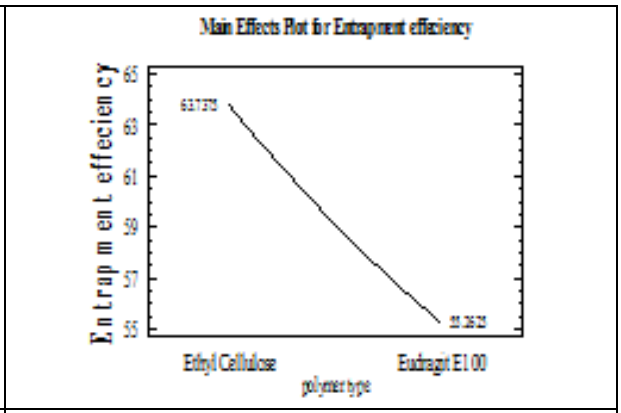

Figure (2): Effect of polymer ratio in entrapment efficiency of RH microspheres

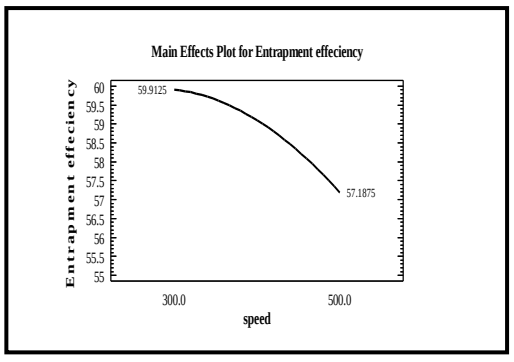

Figure (3): Effect of speed of rotation on entrapment efficiency of RH microspheres

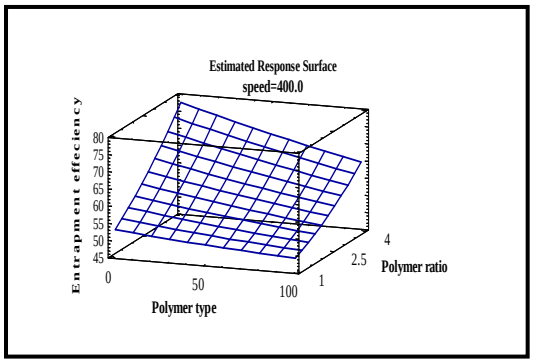

Figure (4): Estimated response surface on entrapment efficiency of RH microspheres

Micromeritic properties of RH microspheres

The prepared RH microspheres were studied for their micromeritic properties, including the angle of repose, bulk and tapped densities, Hausner ratio, and compressibility percent.

a- Angle of repose (Ɵ)

The angle of repose was found to affect the flowability of the particles or granules. The values less than 20° exhibit excellent flowability; the values between 20 and 30° show good flowability; the values between 30 and 34° exhibit passable flowability ; while the values above 34° show very poor flowability **(Bhowmik *et al.*, 2009)**

The values of angle of repose of prepared RH formulae ranged from 19.8° to 29.14° which gives indication that microencapsulation is a good method for improving the flowability.

Concerning the data obtained for the angle of repose for the prepared RH microspheres See table (3), it was found that R HCl - E E 100 (1:4) 400 rpm showed the best value (19.8°) with excellent flowability while formula R HCl - EC/E E100 (1:1) 500 rpm showed the worst value (29.14°) with good flowability.

Marabathuni *et al.*, (2012) observed that the angle of repose of RH microspheres ranged from 22.83° ± 1.71 with excellent flowability to 27.75° ± 3.39 with fairly passable flowability.

So, the RH formulae can be arranged in descending manner as follows: RH-EC/E E100(1:1)500rpm > RH-E E100 (1:1) 400 rpm > RH-E E100 (1:2.5) 500 rpm > RH-EC (1:1) 400 rpm > RH-EC/E E100 (1:1) 300 rpm > RH-EC/E E100 (1:2.5) 400 rpm> RH-EC (1:2.5) 500 rpm > RH-E E100 (1:2.5) 300 rpm> RH-EC100 (1:2.5) 300 rpm> RH-E E100 (1:4) 400 rpm >RH-EC/E E100(1:4)500rpm> RH-EC/E E100(1:4)400rpm > RH-EC (1:4)400rpm which show excellent flowability.

b- The bulk and tap densities

The flow properties of the microspheres were investigated by measuring the bulk density, tapped density and Carr's index **(Sahoo *et al.*, 2005a; Sahoo *et al.*, 2005b)**. Both the bulk and tapped densities were determined with equations described before, as illustrated in table (3). The mean values of both bulk and tapped densities were used to calculate both Hausner ratio and compressibility percent by applying the equations described above. These two parameters are related to the flow properties of the prepared microspheres.

c- The Hausner ratio

The value of the Hausner ratio was found to give indication about the flow properties of microspheres as shown in table (3). The values < 1.25 indicate better flowability than values > 1.25 (**Bhowmik *et al.*, 2009).**According to the data obtained for Hausner ratio for the prepared RH microspheres, it was found that RH - EC (1:4) 400 rpm showed the best value (1.11) while formula RH - EC/E E100 (1:1) 500 rpm showed the worst value (1.22).

So, the RH formulae can be arranged in descending manner as follows: RH-EC/E E100(1:1)500rpm > RH-E E100 (1:1) 400 rpm > RH-E E100 (1:2.5) 500 rpm > RH-EC (1:1) 400 rpm > RH-EC/E E100 (1:1) 300 rpm > RH-EC/E E100 (1:2.5) 400 rpm> RH-EC (1:2.5) 500 rpm > RH-E E100 (1:2.5) 300 rpm> RH-EC100 (1:2.5) 300 rpm> RH-E E100 (1:4) 400 rpm >RH-EC/E E100(1:4)500rpm> RH-EC/E E100(1:4)400rpm > RH-EC (1:4)400rpm which show excellent flowability.

d- Compressibility % (Carr's index)

Compressibility percent is indirectly related to the relative flow rate, a compressible material will be less flowable. The value of the compressibility percent was found to affect the flow properties of the microspheres. The values between 5 and 12 show excellent flowability; the values between 12 and 16 exhibit good flowability; the values between 18 and 21 show fair passable flowability; the values between 23 and 35 exhibit poor flowability; while the values between 33 and 38 exhibit very poor flowability (**Bhowmik *et al.*, 2009)**

In the present study, the maximum compressibility percent for the tested RH formulae was 18.51% for formula RH - EC/E E100 (1:1) 500 rpm which indicate fair

passable flowability and the minimum one was 10% for formula RH - EC (1:4) 400 rpm which indicate excellent flowability, See table (3).

So, the emulsion solvent evaporation technique employed in the present study produced spherical particles with relatively good flowability. Figure (5)

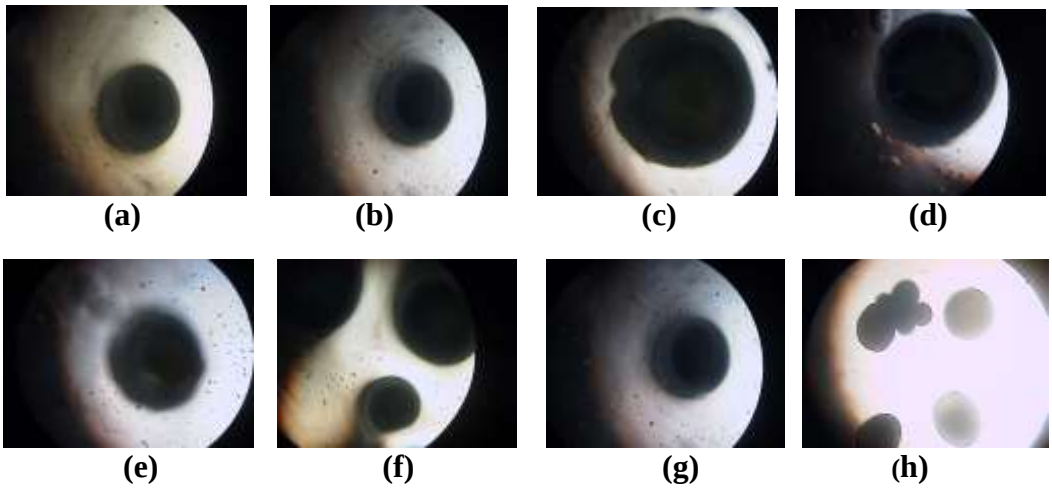

Figure (5): Optical photos of prepared RH microspheres
(a)RH - EC (1:1) 400 rpm**, (b)** RH - EC/E E100 (1:4) 500 rpm ,**(c)** RH-EC/E E100 (1:4) 300rpm, **(d)** RH - EC (1:4) 400 rpm , **(e)** RH - EC (1:2.5) 300 rpm,**(f)** RH - EC/E E 100 (1:2.5), **(g)** RH - E E 100 (1:2.5) 300 rpm**,(h)** RH-E E100(1:1)400 rpm

By combining the rank order of the production yields, the drug contents and the micromeritic properties of prepared RH formulae in table (4), it was found that the best formula was RH-EC (1:4) 400 rpm and the worst one was RH-EC/E E100 (1:1) 500rpm.

Table (2): Production yield and entrapment efficiency of RH microspheres

Formula No	Production yield % (PY)	Entrapment efficiency % (EE)
RH - EC (1:2.5) 300 rpm	86.06	62.1
RH - EC/E E 100 (1:2.5) 400 rpm	98.688	59.1
RH - EC/E E 100 (1:2.5) 400 rpm	98.688	59.1
RH - EC (1:1) 400 rpm	77.88	53.9
RH - E E 100 (1:1) 400 rpm	60.66	47.5
RH - E E 100 (1:2.5) 500 rpm	86.35	55.4
RH - EC/E E100 (1:4) 500 rpm	96.66	66
RH - EC/E E100 (1:1) 300 rpm	87.06	50.8
RH - E E 100 (1:4) 400 rpm	85.58	63.8
RH - E E 100 (1:2.5) 300 rpm	90.35	56.5
RH - EC/E E100 (1:1) 500 rpm	72.34	49.6
RH - EC/E E100 (1:4) 300 rpm	96.466	74.3
RH - EC (1:4) 400 rpm	87.8	79.3
RH - EC/EE 100 (1:2.5) 400 rpm	98.688	59.1
RH - EC (1:2.5) 500 rpm	94.71	61.8

Table (3): Angle of repose, Bulk and Tapped densities of RH microspheres

Formula No	Angle of repose (Θ) (AR)	Bulk density (gm/cm³)	Hausner ratio (HR)	Carr's index (CI)	Tapped density (gm/cm³)
RH - EC (1:2.5) 300 rpm	23.14	0.525±0.005	1.161	13.88	0.610±0.002
RH - EC/E E 100 (1:2.5) 400 rpm	24.05	0.489±0.002	1.184	15.55	0.579±0.001
RH - EC/E E 100 (1:2.5) 400 rpm	24.05	0.489±0.002	1.184	15.55	0.579±0.001
RH - EC (1:1) 400 rpm	28	0.450±0.001	1.190	16	0.536±0.001
RH - E E 100 (1:1) 400 rpm	22	0.325±0.003	1.217	17.85	0.395±0.002
RH - E E 100 (1:2.5) 500 rpm	20.85	0.462±0.004	1.2	16.66	0.555±0.002
RH - EC/E E100 (1:4) 500 rpm	23.7	0.557±0.003	1.155	13.46	0.644±0.001
RH - EC/E E100 (1:1) 300 rpm	27.47	0.398±0.003	1.185	15.62	0.472±0.002
RH - E E 100 (1:4) 400 rpm	19.8	0.531±0.004	1.16	13.79	0.616±0.001
RH - E E 100 (1:2.5) 300 rpm	20.3	0.484±0.003	1.16	14.28	0.564±0.001
RH - EC/E E100 (1:1) 500 rpm	29.14	0.363±0.001	1.22	18.51	0.446±0.003
RH - EC/E E100 (1:4) 300 rpm	21.04	0.599±0.006	1.125	11.11	0.674±0.002
RH - EC (1:4) 400 rpm	20.3	0.627±0.005	1.11	10	0.696±0.001
RH - EC/EE 100 (1:2.5) 400 rpm	24.05	0.489±0.004	1.184	15.55	0.579±0.002
RH - EC (1:2.5) 500 rpm	24.9	0.505±0.005	1.176	15	0.594±0.002

Table (4): Total rank orders concerning the production yields, the entrapment efficiency and the micromeritics properties for RH microspheres

Formula No.	Rank Orders					Total Rank order	
	(PY)	(EE)	(AR)	(HR)	(CI)	Value	RO
RH - EC (1:2.5) 300 rpm	11	5	5	5	5	31	5
RH - EC/E E 100 (1:2.5) 400 rpm	1	7	8	8	8	32	6
RH - EC/E E 100 (1:2.5) 400 rpm	1	7	8	8	8	32	6
RH - EC (1:1) 400 rpm	13	12	12	12	12	49	11
RH - E E 100 (1:1) 400 rpm	15	15	14	14	14	72	14
RH - E E 100 (1:2.5) 500 rpm	10	11	13	13	13	60	13
RH - EC/E E100 (1:4) 500 rpm	4	3	3	3	3	16	3
RH - EC/E E100 (1:1) 300 rpm	9	13	11	11	11	55	12
RH - E E 100 (1:4) 400 rpm	12	4	4	4	4	28	4
RH - E E 100 (1:2.5) 300 rpm	7	10	6	6	6	35	10
RH - EC/E E100 (1:1) 500 rpm	14	14	15	15	15	73	15
RH - EC/E E100 (1:4) 300 rpm	5	2	2	2	2	13	2
RH - EC (1:4) 400 rpm	8	1	1	1	1	12	1
RH - EC/EE 100 (1:2.5) 400 rpm	1	7	8	8	8	32	6
RH - EC (1:2.5) 500 rpm	6	6	7	7	7	33	9

In-vitro buoyancy of RH microspheres

In vitro buoyancy studies reveal that, microspheres still continued to float without any apparent gelation, thus indicating that microspheres can exhibit excellent buoyancies. The relative density of the microspheres is higher at higher polymer concentrations. So, the microspheres having higher polymer concentrations were less buoyant than those with lower polymers concentrations. The formula RH - E100 (1:1) 400 rpm showed highest buoyancy of 92±4.4% while the formula RH-EC/E E100 (1:4) 300rpm showed the lowest buoyancy of 72±1.9%.Table(5)showed the percentage of buoyant microspheres over 12 hr.

Table (5): Rank order of percentage of buoyant microspheres of RH microspheres over 12 hr

Formula No.	% of buoyant microspheres over 12 hr	RO
RH - EC (1:2.5) 300 rpm	79±2.2	11
RH - EC/E E 100 (1:2.5) 400 rpm	83±2.5	7
RH - EC/E E 100 (1:2.5) 400 rpm	83±3.3	7
RH - EC (1:1) 400 rpm	90±4	3
RH - E E 100 (1:1) 400 rpm	92±4.4	1
RH - E E 100 (1:2.5) 500 rpm	86±3.9	5
RH - EC/E E100 (1:4) 500 rpm	78±2.1	12
RH - EC/E E100 (1:1) 300 rpm	88±2.3`	4
RH - E E 100 (1:4) 400 rpm	75±2.2	13
RH - E E 100 (1:2.5) 300 rpm	80±3.1	10
RH - EC/E E100 (1:1) 500 rpm	91±2.7	2
RH - EC/E E100 (1:4) 300 rpm	72±1.9	15
RH - EC (1:4) 400 rpm	73±2.8	14
RH - EC/EE 100 (1:2.5) 400 rpm	83±1.7	7
RH - EC (1:2.5) 500 rpm	84±3.4	6

In-vitro release of RH microspheres

Microspheres behave like plastic materials **(Ahmed *et al.*, 2001).** Dissolution started as the dissolution medium penetrated through the pores of the microspheres. Dissolution medium dissolved RH as it penetrated the microspheres wall. This produced a saturated drug solution inside the microspheres body. That resulted in a concentration gradient between the interior of the microspheres and the dissolution medium. As dissolution proceeded, the dissolved drug diffused out. In vitro drug release studies also showed a biphasic release pattern for all formulations with an initial brust effect as showed in figures (6-8).

RH is water soluble and its release was prolonged up to 12 hr. The release of RH was retarded due to the hydrophobic and insoluble nature of the polymer used .It was also observed that as the polymer ratio increased, the drug release was decreased as the increased density of the polymer matrix at higher polymer concentration resulted in an increased diffusional path length .This may decrease the overall drug release from the polymer matrix. Figures (12-14) showed the effect of polymer ratio on RH release after 2 hr, 6 hr and 12 hr. Furthermore, smaller microspheres were formed at lower polymer concentration and had a larger surface area exposed to dissolution medium, resulted in faster drug release which is good agreement with **(Mastiholimath *et al.*, 2008; Singh *et al.*, 2011).** The cumulative percentage of drug release after 12 hr ranged from 53.1±1.35 to 99.9±0.51 for the formulae RH-EC (1:4) 400 rpm, RH-E E100(1:1)400 rpm respectively as showed in table(6).
The speed of rotation had a direct effect on the drug release as. showed on figures (9-11)

The polymer type either (EC or E E100 or mixture of the both) affected the release of RH ; as the release of drug from formulae prepared with E E100 was higher than formulae with EC as showed in figures (15-17) showed the effect of type of polymer on the release of RH after 2 hr, 6 hr and 12 hr.

Figures (18-20) showed the multiple responses of polymer type, polymer ratio and speed of rotation on RH release after 2 hr, 6 hr and 12 hr.

Table (6): In-Vitro release of R H from hard gelatin capsules

Formula No	% drug released after the respective time intervals (hr)							
	1	2	3	4	6	8	10	12
RH - EC (1:2.5) 300 rpm	18.9 ±1.24	41.4 ±1.29	43.2 ±1.48	45 ±1.54	47.7 ±0.87	50.4 ±1.36	52.2 ±0.85	54.9 ±2.49
RH - EC/E E 100 (1:2.5) 400 rpm	44.1 ±0.94	46.8 ±0.83	50.4 ±1.28	53.1 ±0.72	57.6 ±1.26	63 ±1.59	66.6 ±1.64	75.6 ±1.58
RH - EC/E E 100 (1:2.5) 400 rpm	44.1 ±0.94	46.8 ±0.83	50.4 ±1.28	53.1 ±0.72	57.6 ±1.26	63 ±1.59	66.6 ±1.64	75.6 ±1.58
RH - EC (1:1) 400 rpm	20.7 ±1.63	43.2 ±1.27	45 ±1.58	55.8 ±1.94	56.7 ±1.75	58.5 ±0.98	60.3 ±0.42	63 ±0.62
RH - E E 100 (1:1) 400 rpm	36 ±2.21	72 ±1.24	81 ±1.99	93.6 ±1.79	94.5 ±1.45	96.3 ±2.29	98.1 ±0.84	99.9 ±0.51
RH- E E 100 (1:2.5) 500 rpm	20.7 ±1.26	53.1 ±1.75	58.5 ±1.45	63 ±1.46	80.1 ±0.76	85.5 ±2.45	90 ±1.25	92.7 ±1.92
RH - EC/E E100 (1:4) 500 rpm	44.1 ±2.29	45.9 ±1.85	49.5 ±1.94	51.3 ±2.34	53.1 ±3.76	54.9 ±1.74	61.2 ±1.92	74.7 ±1.58
RH - EC/E E100 (1:1) 300 rpm	45 ±1.92	48.6 ±1.64	51.3 ±2.62	54.9 ±0.92	62.1 ±0.82	68.4 ±1.75	70.2 ±1.35	77.4 ±1.59
RH - E E 100 (1:4) 400 rpm	36.9 ±1.75	39.6 ±1.93	41.4 ±0.92	44.1 ±0.75	45.9 ±1.64	48.6 ±1.47	53.1 ±0.93	59.4 ±0.86
RH- E E 100 (1:2.5) 300 rpm	40.5 ±2.92	47.7 ±1.42	56.7 ±1.95	59.4 ±1.74	72.9 ±1.82	84.6 ±2.98	85.5 ±0.94	87.3 ±1.62
RH- EC/E E100 (1:1) 500 rpm	47.7 ±1.83	53.1 ±1.95	57.6 ±2.52	62.1 ±0.82	65.7 ±1.72	74.7 ±2.92	79.2 ±1.62	94.5 ±0.82
RH- EC/E E100 (1:4) 300 rpm	40.5 ±1.45	42.3 ±1.96	44.1 ±1.74	47.7 ±1.27	48.6 ±0.65	52.2 ±2.92	54.9 ±0.47	57.6 ±1.52
RH- EC (1:4) 400 rpm	32.4 ±1.37	34.2 ±1.46	39.6 ±1.38	42.3 ±0.61	44.1 ±1.79	45.9 ±0.82	50.4 ±1.73	53.1 ±1.35
RH- EC/EE 100 (1:2.5) 400 rpm	44.1 ±0.94	46.8 ±0.83	50.4 ±1.28	53.1 ±0.72	57.6 ±1.26	63 ±1.59	66.6 ±1.64	75.6 ±1.58
RH- EC (1:2.5) 500 rpm	19.8 ±1.55	42.3 ±1.73	46.8 ±1.79	48.6 ±0.62	50.4 ±1.98	53.1 ±1.37	54.9 ±1.94	60.3 ±1.47

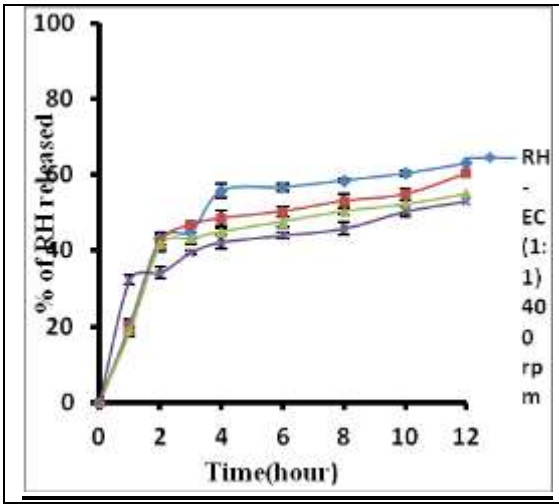

Figure (6): In-vitro release of RH from hard gelatin capsule using EC polymer

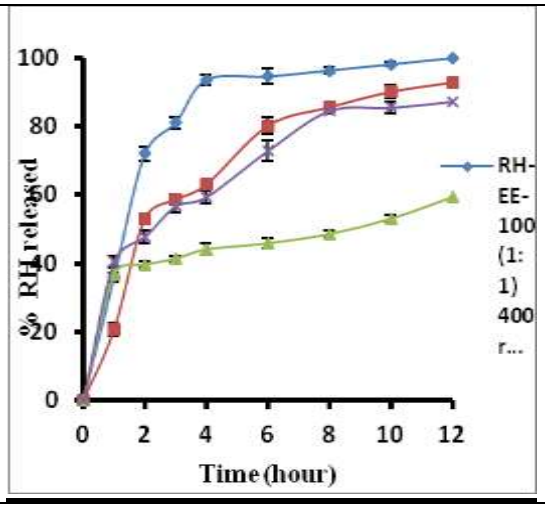

Figure (7): In-vitro release of RH from hard gelatin capsule using E E100 polymer

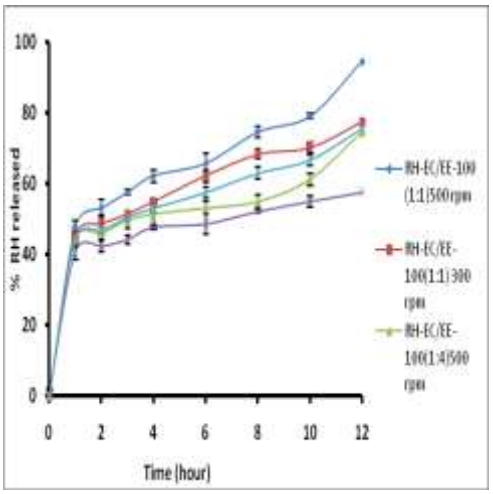

Figure (8): In-vitro release of RH from hard gelatin capsule using EC/EE 100 polymers

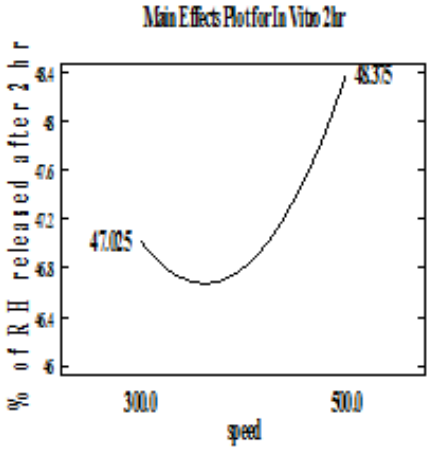

Figure (9): Effect of speed of rotation on RH release after 2

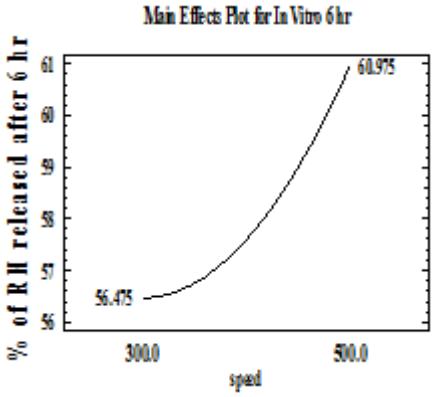

Figure (10): Effect of speed of rotation on RH release after 6 hr

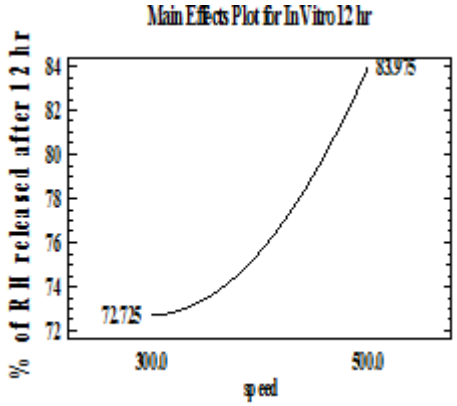

Figure (11): Effect of speed of rotation on RH release after 2 hr.

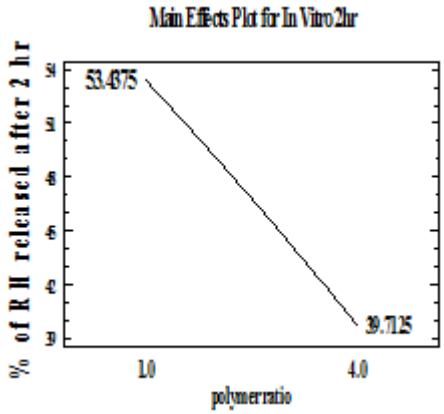

Figure (12): Effect of polymer ratio on RH release after 12 hr

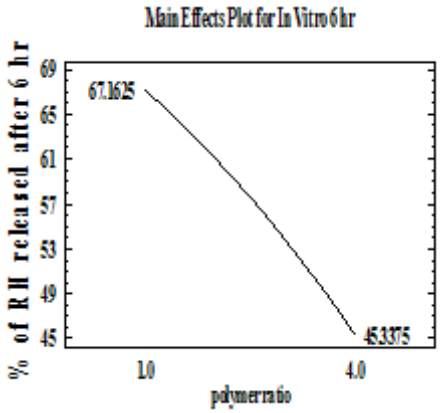

Figure (13): Effect of polymer ratio on RH release after 6 hr

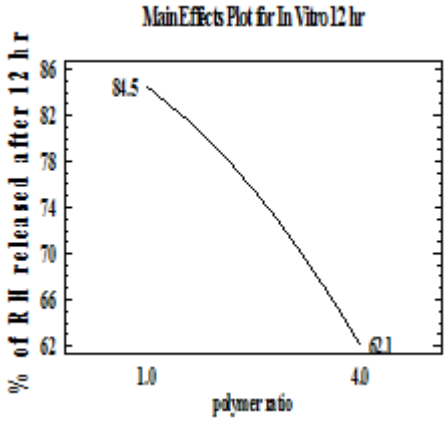

Figure (14): Effect of polymer ratio on RH release after 12 hr

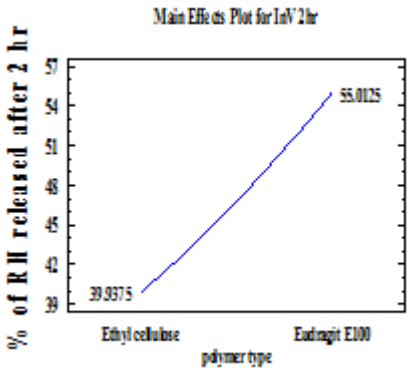

Figure (15): Effect of polymer type on RH release after 2 hr

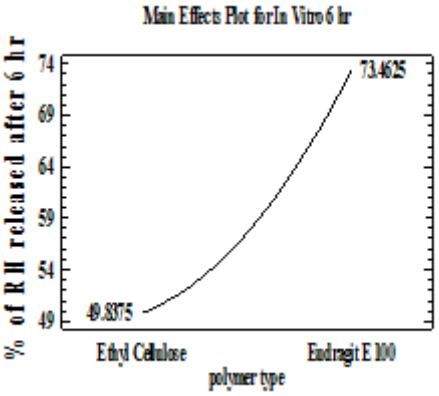

Figure (16): Effect of polymer type on RH release after 6 hr

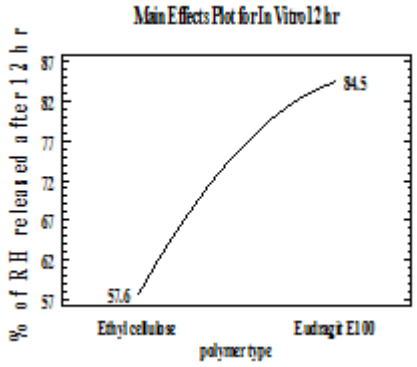

Figure (17): Effect of polymer type on RH release after 12 hr

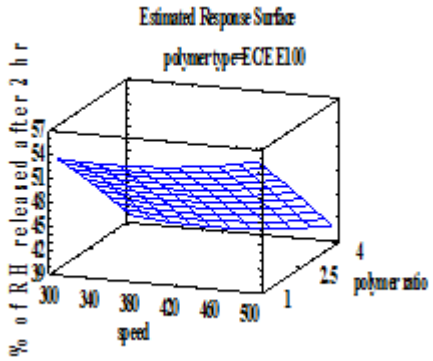

Figure (18): Estimated response surface on RH release after 2hr

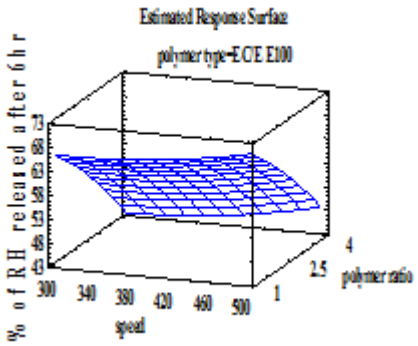

Figure (18): Estimated response surface on RH release after 6 hr

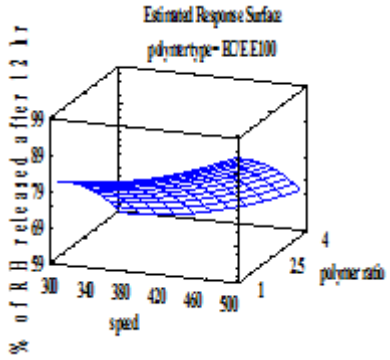

Figure (18): Estimated response surface on RH release after 12 hr

CONCLUSION

- The drug-polymer ratio, the type of polymer employed, and the speed of rotation have reasonable effects on the entrapment efficiency of the prepared RH microspheres
- The micromeritic properties of the prepared RH microspheres which include the angle of repose, bulk density, tapped density, Hauser ratio, and compressibility percent indicate that the produced spherical particles with relatively good flowability which could be easily filled in capsules or compressed in to tablets.
- In vitro release of RH microspheres from hard gelatin capsule was affected by polymer type, polymer ratio and speed of rotation.
- The percentage of buoyant microspheres ranged from 72 to92% over 12 hr
- By combining the production yields, the entrapment efficiency, the micromeritic parameters and the in-vitro release of RH microspheres from hard gelatin capsules it was found that the best formulae in this study was RH-EC/E E100(1:2.5)400 rpm

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صياغة وتقييم الكريات الدقيقة الطافية لعقار رانتيدين ايدروكلوريد لاعطاء عقار منتظم الاتاحة

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الهدف :

الهدف من هذه البحث هو تصميم وصياغة هيدروكلوريد رانيتيدين (**RH**) فى صورة كريات دقيقة طافيه باستخدام تقنيات تبخرمستحلب المذيب باستخدام بوليمرات مختلفة: [إيثيل السليلوز (EC) وEudragit E100 (E100)] مع نسب مختلفه من العقار و البوليمر و بسرعات مختلفة.

طريقة العمل:

تم استخدام تقنية تبخر مستحلب المذيب لتحضير كريات دقيقة طافيه من عقار هيدروكلوريد الرانتيدين ،ثم تم قياس اللختبارات الأتية على الكريات المحضرة و هى:ناتج الأنتاج – كفاءة الدخول- الخصائص الدقيقة للكريات الدقيقة- الطفو فى المختبرو ودراسة الإنطلق المعملى.

النتائج والمناقشة:

أظهرت نتائج دراسة و تحليل الخصائص الدقيقة للكريات للعقار أن كل الصيغ لها تدفق جيد و العائد من الإنتاج يتراوح بين ٦٠.٧٪ إلى ٩٨.٧٪ [أفضل صيغة هى المحتويه على هيدروكلوريد رانيتدين مع خليط من إيثيل السليلوز (EC) و Eudragit E100 بنسبة (١: ٢.٥) بسرعه٤٠٠ دورة فى الدقيقة،ثم أظهرت نتائج كفاءة الدخول انها تتراوح بين ٤٧.٥% إلى ٧٩.٧% [أفضل صيغة هى المحتويه على هيدروكلوريد رانيتدين مع خليط من إيثيل السليلوز (EC) بنسبة (١: ٤) بسرعه٤٠٠ دورة فى الدقيقة و أظهرت نتائج الإختبار المعملى للطفو أنه يتراوح ما بين ٧٢%إلى ٩٢% خلال ١٢ ساعه و الصيغة المثلى تحتوى على هيدروكلوريد رانيتدين مع خليط Eudragit E100 بنسبة (١: ١) بسرعه٤٠٠ دورة فى الدقيقة، و الصيغ التى تحتوى على كثافه أقل أظهرت سلوك طفو ممتاز أحسن من الصيغ التى لها كثافه أعلنز نتائج الإنطلاق المعملى أظهرت زيادة فى نسبة الإنطلاق بتقليل تركيز البوليمر فى الكريات الدقيقة.

من خلال تجميع ما توصل إليه البحث فى الإختبارات التى درست ،اتضح أن الكريات الدقيقة التى تحتوى على هيدروكلوريد رانيتدين مع خليط من إيثيل السليلوز (EC) و Eudragit E100 بنسبة (١: ٢.٥) بسرعه٤٠٠دورة فى الدقيقة هى الصيغة المثلى لتحضير هذا العقار.