

Formulation, Development and Evaluation of Meclozine Hydrochloride Microspheres

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Abstract

Microspheres of meclozine hydrochloride (*MCZ HCl*) were formulated in order to prolong the residence time at the absorption site by intimate contact with the mucous membrane. The microspheres were prepared by orifice-ionotropic gelation method using bioadhesive polymers such as xanthan, sodium, carboxy methyl cellulose (*Na-CMC*) and hydroxy propyl methylcellulose (*HPMC k15*) in combination with different ratio of sodium alginate. Totally nine different formulations of *MCZ HCl* were prepared by using the above polymers. The microspheres were evaluated for percentage yield, entrapment efficiency, particle size analysis, surface morphology (scanning electron microscopy), differential scanning calorimetry (*DSC*), swelling index, drug content and in-vitro dissolution study. The relative bioavailability of the optimized microspheres was compared with commercially available product after oral administration on healthy human volunteers using a randomized, cross-over design. The results revealed that mean particle sizes of the microspheres ranged from 565 to 649 μm and the efficiency of entrapment ranged from 53.46% to 81.58%. SEM photomicrograph showed microspheres with rough surface and spherical in shape. The *DSC* analysis revealed that the drug was uniformly distributed in the microspheres. The optimized microspheres exhibited a slow release over 8 hours. The pharmacokinetic data of the optimized microspheres formula showed prolonged t_{max} , and improved the relative bioavailability by 146.47% compared with commercially available tablets.

Keywords: Meclozine HCl; Sodium alginate; Microspheres; Chitosan; Pharmacokinetics

Introduction

Meclozine hydrochloride (*MCZ HCl*) is a first-generation antihistamine of the piperazine class drug that possesses anticholinergic and antispasmodic effect; it is often prescribed for vertigo, dizziness, motion sickness Meniere's disease, nausea and vomiting during pregnancy [4]. *MCZ HCl* is practically insoluble in water, when administered orally, slow and incomplete absorption occurring from the gastrointestinal tract. Microspheres can control the delivery of drugs from days to months therefore reducing frequent administrations and improving patient compliance and comfort. Different release profiles with desired release rates can be achieved by selecting polymers with different degradation mechanisms [1]. Microspheres improve the bioavailability due to high surface to volume ratio and more contact time with mucous layer [2,3]. Use of natural and thus biodegradable polymers to achieve desired release profile is widely accepted practice in pharmaceutical formulation. In this experimental work, cellulose derivatives like chitosan and sodium alginate were used to prepare microspheres. Sodium alginate is used in combination with different polymers for sustained drug delivery of *MCZ HCl*. Sodium alginate (*SA*) is a naturally occurring polysaccharide which can be easily cross-linked into a solid matrix by replacing the sodium ions from the guluronic acids with di- or tri-valent cations [5] and chitosan that has with excellent biodegradable and biocompatible characteristics [6,7].

The aim of this study is to develop novel *MCZ HCl* microspheres that sustained the release of *MCZ HCl* and evaluate the effect of polymer type and the ratio of polymer to sodium alginate on drug release.

Materials and Methods

Materials

Meclozine hydrochloride, kindly supplied from Chemical Industries Development (*CID*) Co. (Cairo, Egypt). Sodium alginate with medium

viscosity grade (1.05-1.15 *Pa s*) and hydroxyl propyl methylcellulose k_{15} were kindly provided by Pharco Group Pharmaceutical Co., Alexandria, Egypt. Xanthan gum and *Na-CMC* were purchased from Sigma, USA. Isopropyl alcohol, calcium chloride from *ADWIC*, El-Nasr Pharmaceutical Chemicals Co, Cairo, Egypt. Disodium hydrogen phosphate, potassium dihydrogen phosphate (E Merck, Darmstadt, Germany). All other ingredients were of analytical grade.

Preparation of microspheres

Aqueous solution of sodium alginate with xanthan gum, *Na-CMC* and *HPMC k₁₅* in the ratio of 1:1, 3:1, 5:1 were prepared as mentioned in Table 1, fixed concentration of drug was dispersed in 1% chitosan solution then mixed with (5% *w/v*) calcium chloride solution in water. Polymers solution was dispersed drop wise using a syringe with a needle (0.9 mm diameter) into chitosan-calcium chloride solutions with continuous stirring using a magnetic stirrer (Jenway 1000, England) at 1000 rpm for 10 minutes. Microspheres formed immediately and were left into the original solution for 24 hrs to ensure internal gelation; they were filtered, washed with isopropyl alcohol and finally dried at 40°C in an incubator (Hereaus, Germany) for 24 hours [8-10].

Characterization of the prepared microspheres

Determination of percentage yield: The percentage yield of each

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Formulation number	Polymer type	SA : Polymer ratio	Chitosan	Cross linking agent concentration (CaCl ₂)
Formula 1	Xanthan gum	1:1	1%	5%
Formula 2	Xanthan gum	3:1	1%	5%
Formula 3	Xanthan gum	5:1	1%	5%
Formula 4	Na-CMC	1:1	1%	5%
Formula 5	Na-CMC	3:1	1%	5%
Formula 6	Na-CMC	5:1	1%	5%
Formula 7	HPMC- k ₁₅	1:1	1%	5%
Formula 8	HPMC- k ₁₅	3:1	1%	5%
Formula 9	HPMC- k ₁₅	5:1	1%	5%

Table 1: Formulation of various batches for meclizine HCl microspheres.

batch was calculated in terms of percentage yield using the following equation [11].

$$\% \text{ Yield} = (\text{practically obtained yield/theoretical yield}) \times 100 \text{ (equation 1)}$$

The practically obtained yield was determined by weighing all the formed microspheres, which were obtained by ionotropic gelation method, while the theoretical yield was determined by calculation assuming that the entire drug and polymer were used for microencapsulation and no loss occurs.

Determination of the entrapment efficiency: Weighed amounts of each microspheres formulation (50 mg) was dissolved in methanol, sonicated for 10 min and the drug content was determined spectrophotometrically at λ_{232} nm. Entrapment efficiency of microspheres was calculated as follows:

$$\text{Entrapment efficiency} = \text{actual drug entrapped/theoretical drug content} \times 100 \text{ (equation 2)}$$

Particle size analysis: Particle size of microspheres were determined by using an optical microscope under regular polarized light, and the mean particle size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer [12].

Surface morphology of microspheres: The surface morphology of the microspheres was examined by scanning electron microscope (Philips XL30, Netherlands) operated at 4-25 KV on samples gold-sputtered for 120 s at 10 mA, under argon at low pressure.

Thermal analysis using differential scanning calorimeter (DSC): The thermal properties of the drug, unloaded microspheres and loaded microspheres were examined using differential scanning calorimeter (Shimadzu DSC-50, Japan). The samples include pure MCZ HCl, physical mixture (drug, sodium alginate, and chitosan) and MCZ HCl loaded alginate microspheres were placed in flat-bottomed aluminium pan and heated at a constant rate of 5°C/min, under nitrogen gas at a flow rate of 25 ml/min. Data collection was carried out at a temperature range of 0-300°C.

Swelling index (SI): The SI of the microspheres is an indication of the capacity of the microspheres to absorb water and swell. For estimating swelling index, 100 mg of the microspheres were weighed then suspended in HCl (pH 1.2). After 10 hours microspheres were removed, surface water trapped with tissue paper and re-weighed [13,14].

$$SI = [\text{weight of wet microspheres/weight of dry microspheres}] \times 100 \text{ (equation 3)}$$

Drug content: 10 mg of the prepared microspheres were dissolved

in 10 ml methanol and the solutions were filtered and diluted then drug content was determined by UV spectrophotometer at λ_{232} nm. The drug concentration was calculated from the calibration curve.

In vitro dissolution study: The dissolution test was carried out using USP dissolution tester apparatus II (ERWEKA DT 700, Germany) in simulated gastric fluid of pH 1.2 was used for 2 hrs and phosphate buffer of pH 6.8 for 6 hrs as dissolution media. The paddles were rotated at a speed of 50 rpm. Capsules filled with amount of microspheres equivalent to 25 mg of MCZ HCl were placed in the cylinder and an aliquot of 5 ml was collected at predetermined time intervals and replaced with fresh dissolution medium. The samples were filtered by passing through 0.45 μ m membrane filters (Millipore, USA) and analysed spectrophotometrically at λ_{232} nm. The experiments were done in triplicate.

Pharmacokinetic study on human volunteers

Study design and subjects: The study was carried out to compare the pharmacokinetics of MCZ HCl from a microspheres formula (F9) to the marketed, conventional Dramamine® 25 mg tablet following the administration of a single dose of MCZ HCl, using two-way open-label randomized crossover study. The study was carried out on six healthy human volunteers (age: 20-40 years; average weight: 75 kg and median height: 183 cm). Health status of the volunteers was confirmed by laboratory analysis and physical examinations. Each volunteer signed an informed written consent and was fully informed with all the data concerning the drug. The study protocol was approved by research ethics committee, Faculty of Pharmacy, Banisueif University and the protocol complies with the declarations of Helsinki for humans. The drug was administered orally after overnight fasting and washout period of 1 week. The study was performed on two phases: phase I; all volunteers received Dramamine® 25 mg tablets, phase II; all volunteers received F9 microspheres which contain an amount equivalent to 25 mg MCZ HCl. Blood samples (5 ml) were collected after 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hrs after dose administration. All blood samples were instantly centrifuged at 3000 rpm for 10 min (Hettich EBA 21 Centrifuge, Germany), and the plasma samples were frozen and stored at -20°C till drug analysis. The volunteers' blood pressure, heart rate and adverse reactions were routinely monitored.

Mathematical modeling of MCZ release: The release profiles of MCZ from microspheres can be modeled mathematically to obtain information concerning the release mechanism. The release data obtained were fitted to different kinetic models: zero-order³⁴, first-order³⁵, Higuchi³⁶ and Korsmeyer-Peppas models [19] which are often used to describe the drug release behavior from the microspheres.

Assay of MCZ HCl in human plasma

Chromatographic conditions: The plasma concentration of MCZ HCl was determined using a modified HPLC-MS/MS method of Wang *et al.* [15] for the determination of MCZ HCl in plasma. The HPLC apparatus consisted of isocratic pump LC-10 AS and a UV/VIS detector SPD-10A connected to a C-R6A Integrator (Shimadzu, Koyoto, Japan). The analytical column was ponapak C18 HPLC column, 4.6 \times 250 I.D mm, particle size 125 μ A (Waters Associates, Ireland). The mobile phase composed of acetonitrile and 0.2 % formic acid containing 2 mM amino acetate in a ratio 1:1. The mobile phase flow rate was 1 ml/min. The system was operated at ambient temperature and the detection wavelength was 231 nm.

Pharmacokinetic parameters and statistical analysis: The maximum drug concentration (C_{max}) and the corresponding time (t_{max})

were derived from the individual plasma concentration-time curves. The area under the curve was calculated by using WinNonlin[®] (version 1.5, Scientific consulting, Inc., Cary, NC, USA).

Pharmacokinetic characteristics from plasma data following administration of the two treatments were estimated for each subject using WinNonlin[®]. Non-compartmental analysis was used and the maximum drug concentration (C_{max}) and the corresponding time (t_{max}) were determined. The level of absorption from the microspheres formulation (F9) relative to the reference was calculated as the relative bioavailability by using the formula given below:

$$\text{Relative bioavailability (\%)} = (AUC_{0-24} / AUC_{0-24} \text{ reference}) 100 \text{ X.}$$

Results and Discussion

Micromeritic characterization of microspheres

Micromeritic characterization of microspheres was determined by measuring the angle of repose, Carr's index and Hausner factor. The values of angle of repose were found between (20° to 31°) which indicates optimum flow properties for filling into the capsules and all the batches of microspheres were found to fulfill with this in respect of flowability (Table 2) and thus it was possible to fill the microspheres into the capsules.

Percentage yield

Percentage yield of different formulations were calculated and the % yield was found between 65.26 and 84.63% (Table 3). The results indicated that sodium alginate: polymer (5:1) gives better percentage yield for MCZ HCl microspheres than the other ratios 3:1, and 1:1. Also the formulations contain HPMC K₁₅ gave higher yield than that of xanthan gum, and the lowest yield was obtained from formulations containing Na-CMC.

The entrapment efficiency

The entrapment efficiency for the prepared formulation was in the

range of 53.46-81.58% (Table 3). The entrapment efficiency increased progressively with increasing the concentration of sodium alginate which could be attributed to the formation of larger microspheres that entrapped more amount of drug. This may be attributed to the greater availability of active calcium-binding sites in the polymeric chains and, consequently, the greater degree of cross-linking as the quantity of sodium alginate increased [16,17]. The incorporation efficiencies were also higher with the formulations containing HPMC k₁₅. The formulations containing Na-CMC had less amount of drug entrapment which may be due to the higher viscosity of Na-CMC.

The particle size and surface morphology of the prepared microspheres

The mean particle size of the different formulations of the prepared microspheres was between 565 and 692 μm (Table 3), it was observed that the particle size increase with increasing in the concentration of sodium alginate ratio as shown in the formulations 3, 6 and 9 that contain the highest ratio of sodium alginate to polymer (3:1). This could be attributed to the increase in the relative viscosity at high concentration of the alginate and formation of large droplets during addition of the polymer solution to the gelling agents.

The SEM photomicrographs of the microspheres are shown in Figure 1, the morphology of the prepared microspheres was found to be almost spherical in shape and have rough surface.

Differential scanning calorimetry

The DSC thermograms of pure drug, unloaded alginate microspheres and drug loaded alginate microspheres are shown in Figure 2. MCZ HCl exhibited a sharp endothermic peak at 206°C corresponding to its melting point. The peak of the drug in the physical mixture was observed that the large endothermic peak of pure drug was a bit smaller and shifted to 208.94°C in the physical mixture revealing its unchanged nature. This indicates no chemical or physical interaction between the drug and the polymer structure. The melting endotherm of MCZ HCl

Formulation number	Bulk density	Tapped density	Carr's index (%)	Hausner's factor	Angle of repose (± S.D)
Formula 1	0.355	0.465	23.66	1.309	24.37 ± 0.32
Formula 2	0.387	0.491	21.18	1.268	23.99 ± 0.19
Formula 3	0.427	0.501	14.77	1.173	26.49 ± 0.28
Formula 4	0.361	0.472	23.52	1.307	28.53 ± 0.25
Formula 5	0.296	0.368	19.57	1.243	30.02 ± 0.33
Formula 6	0.311	0.372	16.40	1.196	31.32 ± 0.26
Formula 7	0.342	0.427	19.91	1.248	24.35 ± 0.17
Formula 8	0.325	0.396	17.93	1.218	22.38 ± 0.20
Formula 9	0.328	0.392	16.33	1.195	20.05 ± 0.24

Table 2: Micrometrics characterization of various microspheres formulations.

Formulation number	Yield value	Encapsulation efficiency (%)	Swelling index (S)	Drug content (± S.D)	Particle size μm
Formula 1	69.84	67.96	1.42	99.45 ± 5.16	580.82 ± 0.16
Formula 2	73.13	70.25	1.49	97.67 ± 4.32	624.14 ± 0.19
Formula 3	79.79	74.66	1.54	100.3 ± 3.84	692.96 ± 0.27
Formula 4	65.26	53.46	1.31	97.56 ± 4.99	643.53 ± 0.34
Formula 5	68.67	58.60	1.37	99.45 ± 4.87	670.37 ± 0.26
Formula 6	72.05	58.46	1.40	97.67 ± 2.94	694.62 ± 0.14
Formula 7	74.32	61.38	1.44	98.28 ± 5.11	565.32 ± 0.11
Formula 8	80.38	75.63	1.55	99.05 ± 3.64	585.07 ± 0.29
Formula 9	84.36	81.58	1.62	98.81 ± 4.36	604.55 ± 0.16

Table 3: Physicochemical characterization of various microspheres formulations.

Formulation	Zero order	First order	Higushi	Peppas equation	(n) Values peppas equation
Formula 1	0.883	0.961	0.992	0.981	0.472
Formula 2	0.891	0.934	0.985	0.974	0.463
Formula 3	0.912	0.927	0.988	0.967	0.452
Formula 4	0.935	0.945	0.993	0.985	0.472
Formula 5	0.902	0.947	0.979	0.977	0.483
Formula 6	0.969	0.955	0.981	0.969	0.491
Formula 7	0.954	0.972	0.993	0.881	0.484
Formula 8	0.911	0.962	0.962	0.891	0.492
Formula 9	0.965	0.942	0.982	0.965	0.40

Table 4: Correlation coefficient (R^2) values of various kinetic models used for analysis of the release data of Meclozine HCl microspheres and (n) values in Peppas Equation

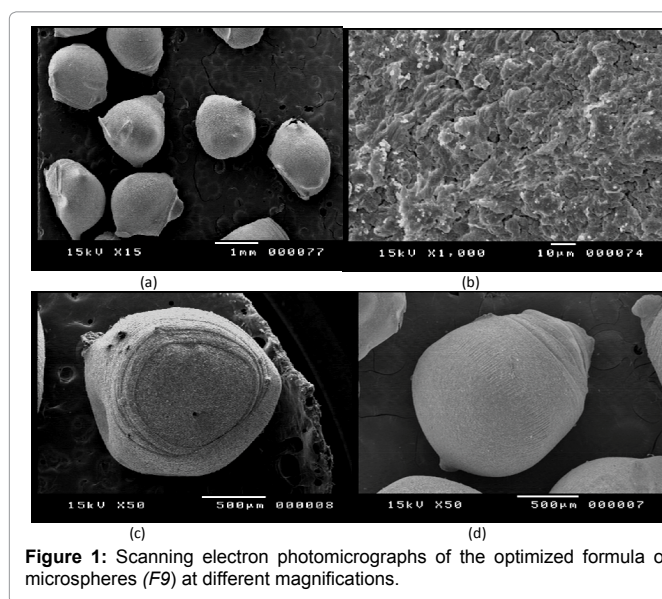


Figure 1: Scanning electron photomicrographs of the optimized formula of microspheres (F9) at different magnifications.

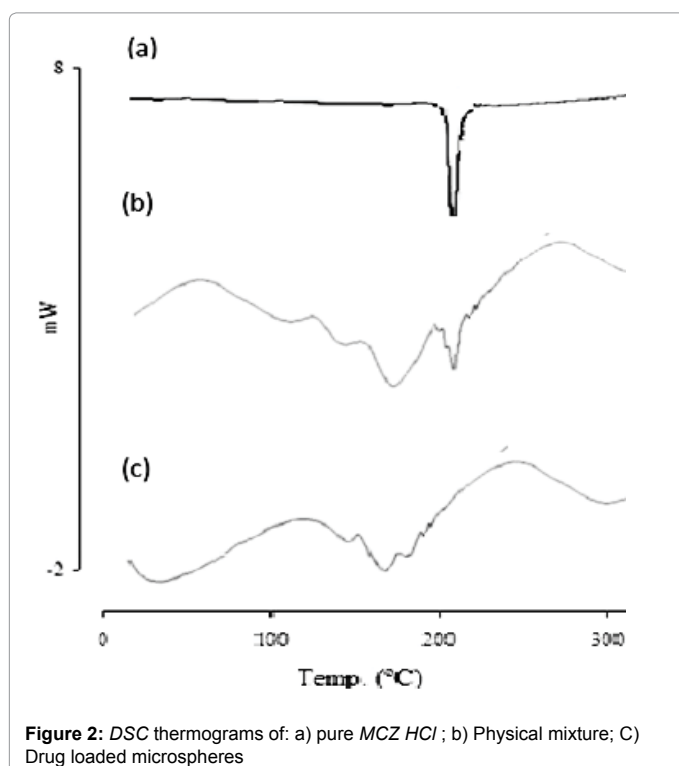


Figure 2: DSC thermograms of: a) pure MCZ HCl; b) Physical mixture; C) Drug loaded microspheres

was not observed in the drug loaded microspheres which indicates that MCZ HCl was uniformly dispersed and present in an amorphous state in the polymeric matrix [18-23].

Swelling study

It was found that by the increasing of alginate concentration the swelling index increase this was due to the high absorption capacity of alginate. All microspheres began to swells presumably due to an increase in the electrostatic repulsive forces at a pH above the pK_a of the uronic acid groups on the alginate [18]. Also swelling of the dry microspheres can be attributed to the hydration of the hydrophilic groups of alginate and chitosan. In this case free water penetrates inside the microspheres in order to fill the pores among polymer chains, contributing to a greater swelling degree [18].

In-Vitro drug release

It is observed from the cumulative drug release profile (Figure 3) that the more sustained effect occurs with the increase in the concentration of sodium alginate which may attributed to the formation of larger microspheres which in turn increase the diffusional path length that delayed the rate of drug release. F9 containing 5% w/v sodium alginate with HPMC k_{15} , showed controlled release patterns of drug, the release was 82.45% after 8 hours indicating the appropriate choice of the formulation variables.

In-Vitro drug dissolution kinetics

For understanding the mechanism of drug release the *in-vitro* drug dissolution data obtained was fitted to various mathematical models such as zero order, First order, Higuchi and Krosmeier-Peppas model.

The kinetic data were analysed of all the formulations and the coefficient of determination (R^2) was used as an indicator of the best fitting for each model. From Table 4 it was seen that the highest correlation coefficient (R^2) was obtained for Higuchi model, this indicates that release of drug from prepared microspheres formulation followed diffusion mechanism [20,21]. Also, kinetic treatment results revealed that the n values were less than 0.5 for the same formulae that confirmed Fickian diffusion mechanism for the release of MCZ from the prepared microspheres [22].

Pharmacokinetic study in human volunteers

F9 was selected for the Pharmacokinetic study according to the micromeritics results, physicochemical characterization and *in-vitro* results. The mean plasma concentration-time data of MCZ HCl following the administration of the marketed Dramamine[®] 25 mg tablet and formula (F9) is shown in Figure 4. The pharmacokinetic results are shown in Table 5, against marketed Dramamine[®] 25 mg tablet the study revealed that the administration of MCZ HCl as microspheres

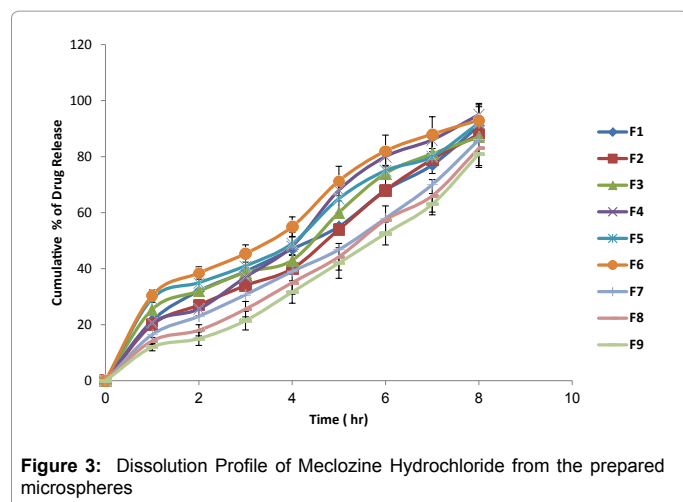


Figure 3: Dissolution Profile of Meclozine Hydrochloride from the prepared microspheres

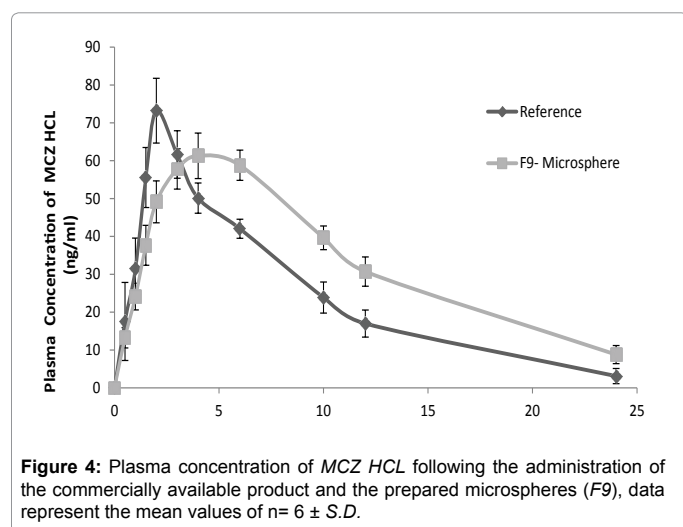


Figure 4: Plasma concentration of MCZ HCL following the administration of the commercially available product and the prepared microspheres (F9), data represent the mean values of n= 6 ± S.D.

Pharmacokinetic parameter	Formula	
	commercially available product	F9 microspheres
$C_{p_{max}}$ (ng/ml)	70.34 ± 2.265	61.29 ± 6.01
t_{max} (hr)	2.17 ± 0.48	4.66 ± 0.94
$AUC_{(0-24)}$ (ng.hr/ml)	572.37 ± 68.34	787.25 ± 89.14
$AUC_{(0-\infty)}$ (ng.hr/ml)	594.3509 ± 73.14	870.2867 ± 97.23
% Relative Bioavailability	-	1.465%
$*t_{1/2}$ (hr)	4.8833 ± 0.51	6.5438 ± 0.64
MRT (hr)	7.7589 ± 1.13	10.9479 ± 1.14

Table 5: Mean pharmacokinetic parameters of MCZ HCL following the oral administration of a single dose (25 mg) of the commercially available product and the prepared microspheres.

can improve the relative bioavailability compared to the marketed oral tablet. The t_{max} of MCZ HCL microspheres were 4.66 ± 0.94 h which is significantly higher than the conventional tablets 2.17 ± 0.48 h. This can be attributed to the retardation of the absorption through increase the contact time at the absorption site and increase the mean resident

time (MRT) of the drug. The increase in the mean t_{max} and the decrease in the mean C_{max} compared with the marketed tablet confirmed controlled-release effect of the microspheres formulations. The mean AUC_{0-24} was found to be 787.25 ± 89.14 ng h/ml for F9 compared with 572.37 ± 68.34 ng h/ml for marketed tablets. From these results, it was found that, the relative bioavailability of MCZ HCL from the optimized formula was 146.5% compared to marketed tablets, which may be due to the increasing in the contact time with the gastric mucosa by the polymers, lead to prolongation in the gastric emptying rate that led to a longer absorption and improving the bioavailability.

Conclusion

The above observations suggested that the MCZ HCL can be developed as drug delivery system with sodium alginate and HPMC k_{15} using calcium chloride as cross linking agent and 1% chitosan as polymer. The microspheres used as drug delivery system for MCZ HCL was successfully prepared by inotropic gelation method and it was found to be a promising formula in the development of a novel sustained drug delivery that help to reduce the dose of the drug and improve its bioavailability.

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