Drotaverine hydrochloride gastroretentive floating mini-tablets: Formulation, in-vitro and in-vivo evaluation

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ABSTRACT

Drotaverine hydrochloride (DRH) is an antispasmodic drug which has a short residence in the intestine during diarrhea that prompts poor bioavailability and frequent dosing. The aim of the present study was to increase the gastric residence time and sustain the release of DRH so increasing patient compliance. Nine floating mini-tablets of DRH were prepared employing different amounts of sodium alginate and sodium bicarbonate by wet granulation technique adopting 3^2 factorial design. The prepared formulae were evaluated for various physical parameters, floating behaviors and in vitro release studies. Formula FF9 (sodium alginate 200 mg and sodium bicarbonate 120 mg) showed optimum floating behavior (floating lag time 49.1 $\pm$ 5.3 s and total floating time $>$ 24 h) and optimum sustained release for DRH (7.60 $\pm$ 1.25% after 0.5 h and 78.14 $\pm$ 3.10% after 12 h). The candidate formula with the highest desirability value (0.942) was evaluated for its bioavailability compared to the marketed product. Statistical analysis revealed significant increase in $AUC_{(0-\infty)}$ 3311.31 $\pm$ 182.18 ng h/ml with delayed T_{max} compared to 1589.54 $\pm$ 127.97 ng h/ml for the marketed product. The results revealed that FF9 could be a promising candidate for gastroretentive drug delivery system for DRH.

1. Introduction

Drotaverine hydrochloride (DRH) is an antispasmodic drug used for smooth muscle spasm and pain associated with gastrointestinal colics, renal colics, biliary colics, irritable bowel syndrome, postsurgical spasm, and uterine neck spasm [1,2]. For decreasing the number of dosing of DRH, normal sustained released dosage forms were excluded due to hypermotility of the intestine accompanied by diarrhea which expels anything in the intestine including the dosage form thus decrease drug's bioavailability and action. An alternative approach is to increase the efficacy of the drug by extending its residence in the stomach through the preparation of gastroretentive dosage form. There are different techniques used to design gastroretentive dosage forms including floating systems, high density systems, expandable systems, superporous hydrogel systems, bioadhesive systems and magnetic systems [3]. Floating drug delivery systems are those systems having a bulk density lower than that of gastric fluids and therefore remain buoyant on the stomach contents to prolong the gastric retention time and increase the overall bioavailability of the drug. These systems can be either effervescent or non-effervescent in nature. In effervescent

systems, gas generating excipients, such as sodium bicarbonate and acidic ingredients are used to produce CO_2 in presence of gastric acid [4].

Most of the floating drug delivery systems previously described are single unit systems such as tablets and capsules. Multiple unit floating drug delivery systems, for example, pellets or mini-tablets, exhibit several advantages over single unit ones, which comprise avoiding all or nothing emptying, limit the chance of localized mucosal harm, more expectable drug release kinetics and administration of units with various release profiles [5,6]. Mini-tablets offer an alternative for pellets in view of their relative ease of manufacturing. Besides, they offer dosage forms of equal dimensions and weight with smooth regular surface that could be achieved in a reproducible and continuous way. Mini-tablets could be either filled into hard capsules or compacted into bigger tablets [7]. Furthermore, DRH was previously formulated onto floating gastroretentive tablets as reported by Prakash et al. [8] and onto calcium alginate floating gastroretentive beads as reported by Adel and Elkasabgy [9]. Best to our knowledge, DRH has not been formulated as gastroretentive floating mini-tablets. The aim of the present study was to formulate DRH into floating mini-tablets as gastroretentive system to

control the release of DRH in order to maintain the drug plasma concentration for a longer time, reduce the frequency of dosing and improve the patient compliance.

2. Materials and methods

2.1. Materials

Drotaverine hydrochloride (DRH) and Spasmocure® tablets were kindly supplied by AlphaAmoun (Egypt). Sodium alginate and carbopol 934 were purchased from Sigma-Aldrich (USA). Sodium chloride, sodium bicarbonate, citric acid and lactose were obtained from El-Nasr (Egypt). Magnesium stearate was procured from Alba (India). Hydrochloric acid 37 % was brought from Honeywell (Germany). Hard gelatin capsules (size 00) were brought from Arab Gelatin & Pharmaceutical (Egypt). All materials were used as received.

3. Methods

3.1. Experimental design

After initial trials, the amount of sodium alginate (X_1) and sodium bicarbonate (X_2) were identified as variables in order to optimize the levels of these two variables, a 3^2 factorial design was adapted [10]. The design composed of two independent variables with three levels resulting in 9 runs. The percentage of initial drug released after 0.5 h, the percentage of drug released after 12 h, floating lag time and total floating time were selected as dependent variables. Design Expert software (version 7, Stat-Ease Inc., Minneapolis, USA) was used to generate and analyze the statistical experimental design. The line plots analysis was done to study the effect of variables on the responses. The statistical significance of the data was established using analysis of variance (ANOVA) at 95 % confidence interval (P < 0.05). Optimization was performed to find out the level of independent variables (X_1 and X_2) that would yield a minimum value of % initial drug released after 0.5 h, minimum value of % drug released after 12 h, minimum floating lag time and maximum total floating time by applying desirability settings for the most effective formula to achieve the desired prolonged release of drug by expanding the gastric residence time.

3.2. Preparation of the floating mini-tablets

All ingredients were weighed and mixed well except magnesium stearate. The mixture was granulated using isopropyl alcohol. The obtained dough mass was passed through 1250 μm-mesh screen to prepare the granules. Magnesium stearate was then added then the granules were dried for 2 h in an oven at 50 ± 2 °C and kept in a desiccator for 24 h. Dried granules were ground in a mortar and then sieved through 1000 μm-mesh screen. Thereafter, mini-tablets were obtained using a single punch tablet press (Royal artist, Bombay, India) fitted with a 6 mm diameter concave punch [11]. Each dose consisted of 8 mini-tablets filled into hard gelatin capsule (size 00) which are equivalent to 60 mg DRH and packaged in well closed light resistance and moisture proof containers. The detailed composition of the prepared floating mini-tablets is shown in Table 1.

3.3. Evaluation of the pre-compression parameters of powder mixtures

Pre-compression parameters like bulk density, tapped density, angle of repose, Hausner's ratio and Carr's index were measured [12].

3.4. Evaluation of the post-compression parameters of mini-tablets

3.4.1. Weight variation

The weight variation test was conducted by weighing 20 randomly selected mini-tablets individually to calculate average weight and

Table 1
Composition of the prepared drotaverine hydrochloride floating mini-tablets formulae.

Ingredients	Formulae								
	FF1	FF2	FF3	FF4	FF5	FF6	FF7	FF8	FF9
DRH	60	60	60	60	60	60	60	60	60
Sodium alginate	120	160	200	120	160	200	120	160	200
Carbopol 934	40	40	40	40	40	40	40	40	40
Sodium bicarbonate	60	60	60	90	90	90	120	120	120
Citric acid	60	60	60	60	60	60	60	60	60
PVP K30	20	20	20	20	20	20	20	20	20
Lactose	270	230	190	240	200	160	210	170	130
Magnesium stearate	10	10	10	10	10	10	10	10	10

* Each formula has 8 mini-tablets.
** Total weight of each formula is 640 mg (8 mini-tablets).
*** Weight of each mini-tablet is 80 mg.

variation.

3.4.2. Diameter and thickness

The diameter and thickness of ten randomly selected mini-tablets from each formula were measured with a tablet hardness tester (Erweka type; GmbH, Heusenstamm, Germany). The average value and standard deviation of diameter and thickness were calculated.

3.4.3. Friability test

Ten mini-tablets were weighed and placed in the plastic chamber of friabilator (Erweka type; GmbH, Heusenstamm, Germany) and set for 25 rpm for about 4 min and the mini-tablets were removed, dedusted and reweighed. The percentage of friability was calculated

$$Friability\,(\%) = \frac{W\ initial - W\ final}{W\ initial} \times 100$$

where, $W_{initial}$ = weight of the mini-tablets before the test, W_{final} = weight of the mini-tablets after test and % friability of mini-tablets less than 1 % is considered acceptable [13].

3.4.4. Hardness test

The hardness of the mini-tablets was determined using tablet hardness tester (Erweka type; GmbH, Heusenstamm, Germany). Six mini-tablets from each formula and crushing strength that just caused the mini-tablets to break were recorded. The average of 6 records expressed in Kg/cm^2 was calculated [14].

3.4.5. Content uniformity test

Each formula (eight mini-tablets) equivalent to 60 mg DRH was accurately weighed and transferred into 100 ml volumetric flask with 0.1 N HCl (pH 1.2). Subsequently, the solution in the volumetric flask was filtered and suitable dilutions were made and analyzed at 353 nm using a UV–Visible spectrophotometer (Shimadzu UV-1650 PC, Kyoto, Japan). The drug content of each formula was estimated from the standard curve of drug using 0.1 N HCl (pH 1.2) [15].

3.4.6. Floating behavior

The floating behavior was determined by measuring the buoyancy lag time and total floating duration. The mini-tablets were placed in a beaker containing 100 ml of 0.1 N HCl (pH 1.2) maintained at 37 °C. The time required for the mini-tablet to rise to the surface was determined as floating lag time and the time period up to which the mini-tablet remained floating was termed as total floating time or buoyancy time [16,17].

3.4.7. In vitro release of drotaverine hydrochloride from floating mini-tablets

The release of DRH from the prepared floating mini-tablets was

performed for 24 h at a temperature of 37 ± 0.5 °C and stirred at 100 rpm using USP dissolution apparatus II (model 708-DS; Agilent, Waldbronn, Germany). Each formula (eight mini-tablets) equivalent to 60 mg DRH was placed in 1000 ml 0.1 N HCl (pH 1.2) dissolution medium. The amount of DRH released was assayed spectrophotometrically using UV spectrophotometer (Shimadzu UV-1650 PC, Kyoto, Japan) at λ_{max} 353 nm [18] against 0.1 N HCl as blank. The cumulative % of DRH released was calculated at each time interval. For comparison, the DRH release was also performed for the marketed product (Spasmocure® tablets 60 mg DRH). The experiment was done in triplicate (n = 3) [19,20].

3.4.8. Kinetics analysis of the release data

In order to understand the mechanism and kinetics of DRH release, the result of the in vitro release data from floating mini-tablets was fitted to various kinetic equations, such as zero order, first order, Higuchi's model and Korsmeyer-Peppas model. Determination coefficient (r^2) values were calculated for the regression analysis [21].

3.4.9. Differential scanning calorimetry (DSC)

DSC was used to detect any changes of drotaverine hydrochloride characteristic peaks that might occur after mixing with different excipients. The thermal behavior of pure drotaverine hydrochloride drug and drug-excipients mixtures was investigated using differential scanning calorimeter (Shimadzu DSC-60, Kyoto, Japan). Samples (pure drug and drug-excipients mixtures) were heated under nitrogen atmosphere as a carrier gas on an aluminum pan at a flow rate of 30 ml/min and a heating rate 5 °C/min over a temperature range of 20–400 °C [22,23].

3.5. In vivo study of the selected floating mini-tablets

Twelve healthy New Zealand male albino rabbits were divided in this experiment, in a randomized parallel design [24,25]. The study was approved by the research ethics committee for experimental and clinical studies at Faculty of Pharmacy, Cairo University, Cairo, Egypt (serial number: PI 954). The rabbits were randomly allocated to two groups, each group containing six rabbits [26] as followed; group I: each rabbit received the calculated dose of drotaverine hydrochloride of floating mini-tablets as prepared formula FF9 and group II: each rabbit received the calculated dose of drotaverine hydrochloride of marketed product (Spasmocure® tablet). The dose calculated according to human equivalent dose calculation based on body surface area [27,28].

The HPLC method was applied for the determination of DRH in plasma with slight modifications [29]. Samples were assayed using HPLC (Agilent 1260, Waldbronn, Germany) at ambient temperature using a micro-particulate Bondapak column (C18 300 mm × 4.6 mm, particle size 10μ) (Waters Corporation, Massachusetts, USA). The mobile phase consisted of acetate buffer pH 4.5 and acetonitrile (55:45). A flow rate of 2 ml/min was used and the eluent was analyzed with a UV

detector (Agilent 1260, Waldbronn, Germany) at 353 nm. Working standard solutions of DRH were prepared by serial dilution of stock solution (50, 100, 200, 400, 600, 800, 1000 and 2000 ng/ml). Working standard solution of hydrochlorothiazide (HTZ) internal standard was prepared (100 μg/ml). Under the described conditions, the retention times of HTZ and DRH were 2.3 and 6.9 min, respectively. The intra and inter-batch precision and accuracy of the analytical procedure were evaluated after replicating analysis (n = 9) of control samples spiked at three concentration levels for the standard calibration curve. The lower limit of quantification was 397.87 ng/ml. With a linear response across the full range of concentrations from 50 to 2000 ng/ml (R^2 = 0.9995). The pharmacokinetic parameters were calculated using the plasma concentrations where the pharmacokinetic parameters (C_{max}, T_{max}, $AUC_{(0-24)}$ and $AUC_{(0-\infty)}$) and relative bioavailability were measured [30].

4. Result and discussion

4.1. Pre-compression parameters of powder mixtures

All the prepared powder formulae showed values of angle of repose ranging from 25.08 to 30.12° that indicated excellent flow characteristics [31]. Bulk density and tapped density of the prepared powders were found to vary from 0.48 ± 0.20 to 0.56 ± 0.08 gm/ml and 0.51 ± 0.08 to 0.61 ± 0.05 gm/ml, respectively. The values of Hausner's ratio and Carr's index ranged from 1.13 to 1.23 and 13.61to 17.51%, respectively. The results indicate good compressibility of the prepared powders [32].

4.2. Post-compression parameters of mini-tablets

The prepared mini-tablets were light yellow round concave, with smooth surface in both sides with no visible cracks. The mean weight of twenty mini-tablets from each formula ranged between 74.36 ± 1.55 to 82.06 ± 3.42 mg. All the mini-tablets passed weight variation test as the % weight variation was within the Pharmacopoeial limits of ± 10% of the weight. The average thickness of prepared mini-tablets was found to range from 1.87 ± 0.12 to 2.16 ± 0.16 mm while the mean diameter of the prepared mini-tablets was in the range of 5.95 ± 0.10 to 6.09 ± 0.13 mm. The friability percentage ranged from 0.38 ± 0.24 to 0.89 ± 0.10 % that was less than 1 % indicating good mechanical strength according to Pharmacopoeial limits. The mini-tablets showed also no evidence of capping, cracking, cleavage or breaking after being removed from the friabilator. The hardness values ranged from 4.83 ± 0.77 to 7.13 ± 0.58 kg. The hardness values of all compressed mini-tablets indicated good mechanical strength to withstand physical and mechanical stress conditions. Drug content of all mini-tabletۥs formulae showed homogenous drug content within the Pharmacopoeial limits and ranged from 86.25 ± 2.06 to 93.22 ± 0.98 %. Table 2 shows the results of the physiochemical

Table 2
Weight variation, friability, hardness, thickness, diameter, content uniformity and floating behavior of floating mini-tablets formulae.

Formulae code	Weight variation (mg) (Mean ± SD, n = 20)	Friability (%) (Mean ± SD, n = 2)	Hardness (kg) (Mean ± SD, n = 10)	Thickness (mm) (Mean ± SD, n = 10)	Diameter (mm) (Mean ± SD, n = 10)	Content uniformity (%) (Mean ± SD, n = 10)	Floating lag time (sec) (Mean ± SD, n = 3)	Total Floating time (h) (Mean ± SD, n = 3)
FF1	75.51 ± 3.46	0.75 ± 0.12	5.65 ± 0.67	2.11 ± 0.12	6.03 ± 0.14	85.86 ± 2.61	66.30 ± 4.50	>24
FF2	81.53 ± 2.52	0.89 ± 0.10	4.83 ± 0.77	1.87 ± 0.12	5.96 ± 0.11	87.43 ± 3.07	69.60 ± 3.70	>24
FF3	74.36 ± 1.55	0.38 ± 0.24	7.13 ± 0.58	2.16 ± 0.16	6.05 ± 0.15	90.70 ± 3.79	71.50 ± 4.30	>24
FF4	74.91 ± 4.10	0.79 ± 0.12	5.12 ± 1.21	1.96 ± 0.13	6.10 ± 0.12	86.84 ± 2.78	55.40 ± 4.50	>24
FF5	79.35 ± 3.14	0.45 ± 0.39	6.19 ± 0.84	2.09 ± 0.15	5.95 ± 0.10	86.97 ± 3.25	57.60 ± 4.90	>24
FF6	82.06 ± 3.42	0.62 ± 0.24	6.45 ± 0.79	1.95 ± 0.20	6.02 ± 0.13	90.53 ± 3.88	59.90 ± 4.90	>24
FF7	77.21 ± 3.49	0.46 ± 0.22	7.09 ± 0.58	2.01 ± 0.18	6.04 ± 0.14	87.99 ± 2.44	46.80 ± 5.70	>24
FF8	76.78 ± 4.07	0.51 ± 0.27	6.39 ± 0.66	1.93 ± 0.17	6.09 ± 0.13	88.57 ± 2.95	48.20 ± 5.70	>24
FF9	78.09 ± 2.23	0.66 ± 0.34	5.51 ± 0.73	2.02 ± 0.20	6.08 ± 0.11	90.77 ± 3.79	49.10 ± 5.30	>24

properties of prepared drotaverine hydrochloride mini-tablets.

4.3. Floating behavior

The total floating time of all prepared mini-tablets formulae was maintained more than 24 h. That's might be due to the presence of sodium bicarbonate which was used as a gas-generating agent. The sodium bicarbonate is inducing CO_2 generation in the presence of dissolution medium (0.1 N HCl). The gas generated was trapped and protected within the gel formed by hydration of the polymer, thus decreasing the density of the mini-tablets below 1 gm/mL, and the mini-tablets became buoyant [33]. In vitro buoyancy lag time of the mini-tablets from each formula was evaluated and the results ranged from 69.60 ± 3.70 to 46.80 ± 5.70 s. It was observed that the concentration of sodium bicarbonate played an important role in the floating lag time of mini-tablets, the higher the concentration of sodium bicarbonate the lesser the floating lag time in accordance with the results obtained by Nama et al., 2008 [34]. The floating behavior of the prepared mini-tablets is shown in Table 2. Ideally floating gastro-retentive dosage forms should float rapidly after contact with the gastric content to prevent the drug from transiting into the small intestine. In addition, floating duration of the formulae should be maintained till complete drug release took place [17]. Fig. 1 showed the floating behavior of FF1as random example of the prepared mini-tablets formulae in 0.1 N HCl (pH1.2) where the mini-tablet had buoyancy lag time of 66.30 s and floating time more than 24 h and never sank during this period.

The variables, namely; sodium alginate amount (X_1) and sodium bicarbonate amount (X_2) had no significant effect ($p \geq 0.05$) on the total floating time where all mini tablets formulae maintained floating for more than 24 h. It was found that the floating lag time was significantly affected by sodium bicarbonate amount while sodium alginate amount did not significantly affect the floating lag time. A polynomial equation of mean floating lag time was also obtained and shown below in the terms of coded factors:

Floating lag time $= +57.78 – 1.89X_1 + 10.11X_2 - 0.56X_1 X_2$

A positive sign of coefficient indicates that the output increases with an increase in parameter level, and negative coefficient indicates that the output increases with a decrease in parameter level. The floating lag time insignificantly increased with increasing sodium alginate amount that might be due to increasing tablet integrity with increasing sodium alginate amount while it significantly decreased with increasing sodium bicarbonate amount. This might be due to the increase of sodium bicarbonate amount exhibiting faster and higher CO_2 generation decreasing the density of the mini-tablets and the mini-tablets become buoyant [35].

4.4. In vitro release of drotaverine hydrochloride from floating mini-tablets

The in vitro release of DRH from mini-tablets formulae and marketed product (Spasmocure® 60 mg) in 0.1 N HCl (pH 1.2) are illustrated graphically in Fig. 2. The results showed lower percent of DRH released from the prepared mini-tablets when compared to the marketed product (Spasmocure® 60 mg). This might be related to the high viscosity of polymer which could induce the formation of strong viscous gel layer this might lead to decrease the water diffusion into the mini-tablet which could result in the retardation or decrease of the percentage of drug released [36,37]. Whereas, for the marketed product (Spasmocure® 60 mg), more than 90 % of DRH were released within 30 min, the rapid disintegration of the tablet could promote the rapid drug release as dissolution rate is highly dependent on the rate of disintegration process [38].

The in vitro release of DRH from formulae (FF1, FF4 and FF7) prepared using 120 mg sodium alginate were 22.36 ± 1.68, 20.31 ± 1.14 and 18.84 ± 1.24 % after 0.5 h and 96.50 ± 1.89, 94.05 ± 1.59 and 92.61 ± 1.59 % after 12 h respectively while the percentage of DRH released from formulae (FF2, FF5 and FF8) prepared using 160 mg sodium alginate were 18.36 ± 1.02, 16.85 ± 1.08 and 15.14 ± 1.19 % after 0.5 h and 91.03 ± 1.11, 88.01 ± 1.59 and 86.94 ± 2.11 % after 12 h respectively. From the results, the formulae (FF2, FF5 and FF8) showed higher retardation of DRH released due to the higher concentration of sodium alginate when compared to all other prepared formulae (FF1, FF4 and FF7). Regarding FF3, FF6 and FF9, the percentages of DRH released were 11.10 ± 0.98, 9.05 ± 0.98 and 7.60 ± 1.25 % after 0.5 h and 85.84 ± 1.23, 80.55 ± 1.74 and 78.14 ± 3.10 % after 12 h respectively. It was observed that the DRH released was lower for these formulae due to the increased concentration of sodium alginate (200 mg) which could form hydrated gel matrix that created a tortuous diffusion path for the drug, resulting in a sustained release of the drug [39,40]. It was clear that the variable (X_1 and X_2) had a significant effect ($p < 0.05$) on the initial release of DRH after 0.5 h and release of DRH after 12 h from the floating mini-tablets.

A polynomial equation of mean percent of initial release of DRH after 0.5 h and 12 h from floating mini-tablets were also obtained and shown below in the terms of coded factors:

Initial release of DRH after 0.5 h $= +15.52 + 6.76 \times_1 + 1.54 \times_2 -0.026 \times_1 X_2$

Release of DRH after 12 h $= +88.47 + 6.42 \times_1 + 2.58 \times_2 -1.9 \times_1 X_2$

A positive sign of coefficient indicates that the output increases with an increase in parameter level and negative coefficients that the output increases with a decrease in parameter level. The initial release of DRH after 0.5 h and the release of DRH after 12 h from floating mini-tablets significantly decreased with increasing sodium alginate [37,41]. Furthermore, the initial release of DRH after 0.5 h and the release of DRH after 12 h from floating mini-tablets significantly decreased with
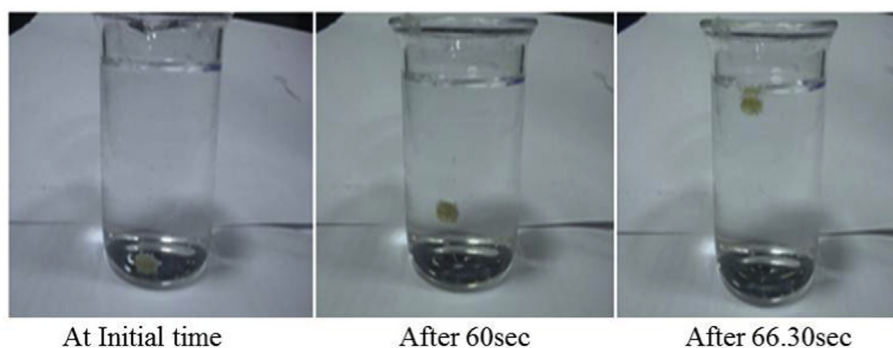

| At Initial time | After 60sec | After 66.30sec |

Fig. 1. Photographs taken during in-vitro buoyancy of mini-tablet in 0.1 N HCl (pH1.2) (FF1).
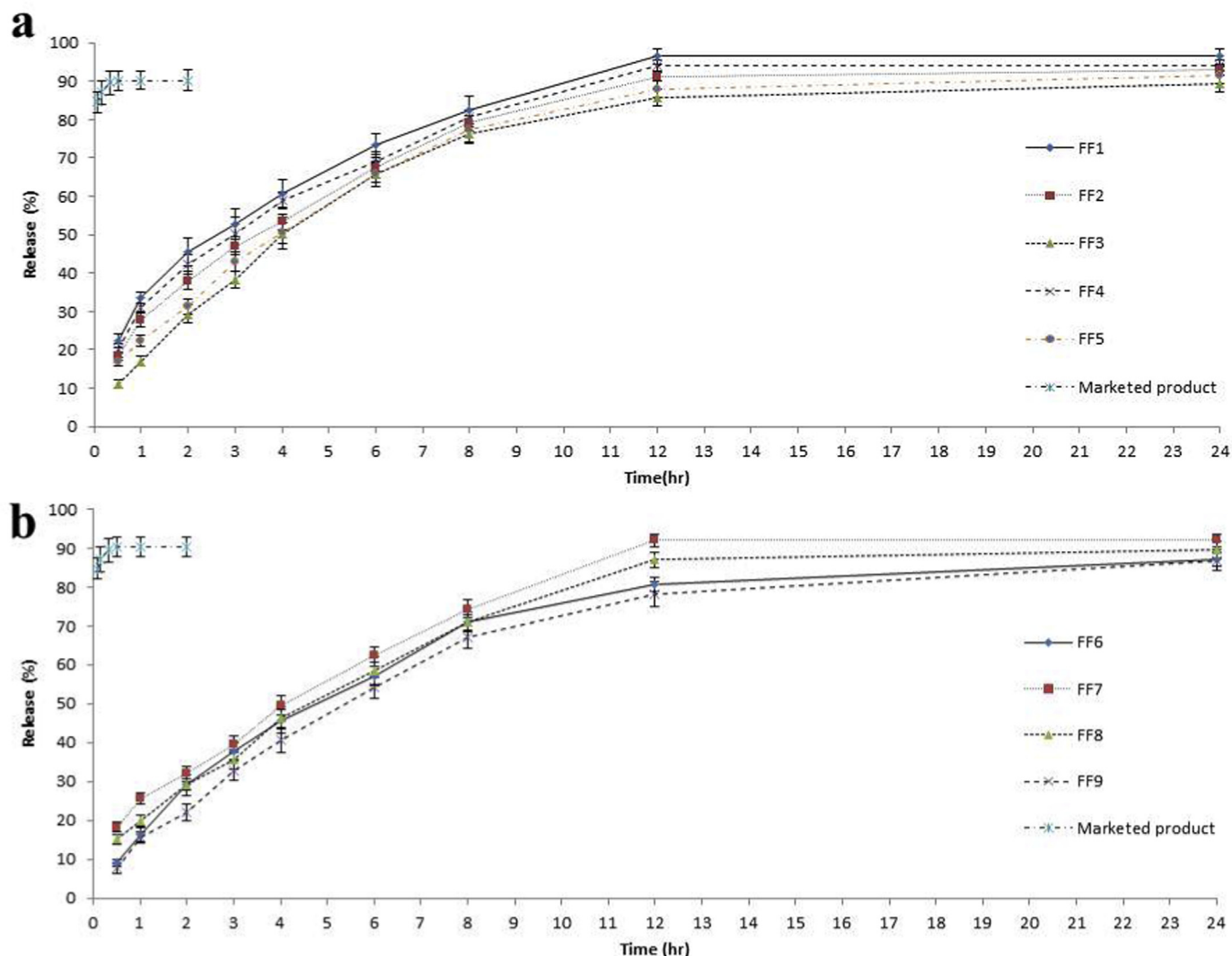
Fig. 2. In vitro release of DRH from the prepared floating mini-tablets formulae and marketed product
a) Mini-tablets formulae (FF1 to FF5) and marketed product in 0.1 N HCl (pH 1.2)
b) Mini-tablets formulae (FF6 to FF9) and marketed product in 0.1 N HCl (pH 1.2).

increasing sodium bicarbonate. This probably might be related to the solubility of the drug. Sodium bicarbonate being alkaline in nature created an alkaline microenvironment around the mini-tablet and the drug was less soluble in alkaline pH which would decrease drug release from the tablet matrix [42,43].

The highest desirability response of the prepared formulae was determined. The aim was to minimize initial DRH released after 0.5 h and after 12 h, maximize total floating time and minimize floating lag time. Among nine formulae prepared FF9 (sodium alginate 200 mg and sodium bicarbonate 120 mg) with desirability value of 0.942 was chosen as a candidate formula for further in vivo studies. This formula had proper physical properties as well as optimum drug release. It showed the lowest percent of DRH after 0.5 h and was able to sustain DRH release more than 12 h where 7.60 ± 1.25 % were released after 0.5 h and 78.14 ± 3.10 % were released after 12 h as well as suitable floating lag time just 49 s.

4.5. Release kinetics of drotaverine hydrochloride from floating mini-tablets

The release of DRH from mini-tablets formulae showed best fitting to Korsmeyer Peppas as shown in Table 3. FF1 formula with "n" value 0.399 exhibited a Fickian model (case I mechanism) while all other formulae with "n" values ranged from 0.455 to 0.693 exhibited a non-Fickian model (anomalous transport), so the release of DRH from these formulae was governed by both diffusion of the drug and dissolution of the polymeric network [44–47]. While the marketed product (Spasmocure® 60 mg) showed best fitting to first order suggesting that the drug release is governed with concentration gradient [48,49].

4.6. Differential scanning calorimetry (DSC)

The differential scanning calorimetry thermograms of pure DRH drug and drug-excipients mixtures are illustrated graphically in Fig. 3. The DSC thermogram of pure DRH powder showed a sharp endothermic peak at 210.90 °C corresponding to its melting point [50]. There is a slight shift in drug excipient mixture indicating no physical interaction between DRH and any of excipients used in mini-tablets formulae.

4.7. In vivo study of the selected floating mini-tablets formula

Plasma concentrations of drotaverine hydrochloride versus time profile following oral administration of floating mini-tablets FF9 and marketed product (Spasmocure® tablet) in rabbits are illustrated in Fig. 4. An equivalent dose of floating mini-tablets formula (FF9) was

Table 3
Coefficient of determination r^2 of DRH release data from the prepared mini-tablets formulae and marketed product according to zero order, first order, Higuchi model and Korsmeyer Peppas model.

Formula code	Zero order r^2	First order r^2	Higuchi r^2	Korsmeyer peppers		Best fit model
				r^2	N	
FF1	0.649	0.847	0.899	0.990	0.399	Korsmeyer Peppas
FF2	0.685	0.872	0.916	0.996	0.532	Korsmeyer Peppas
FF3	0.698	0.865	0.910	0.996	0.619	Korsmeyer Peppas
FF4	0.660	0.839	0.905	0.994	0.455	Korsmeyer Peppas
FF5	0.706	0.887	0.921	0.985	0.624	Korsmeyer Peppas
FF6	0.738	0.904	0.935	0.993	0.659	Korsmeyer Peppas
FF7	0.726	0.847	0.928	0.984	0.668	Korsmeyer Peppas
FF8	0.748	0.886	0.937	0.987	0.693	Korsmeyer Peppas
FF9	0.779	0.932	0.946	0.990	0.625	Korsmeyer Peppas
Marketed product	0.886	0.914	0.698	–	–	First order

administered to one group of rabbits and the other group administered the marketed product (Spasmocure® tablet).

The mean pharmacokinetic parameters are summarized in Table 4. Statistical analysis of the pharmacokinetics parameters showed that there were significant differences ($p < 0.05$) between the values of C_{max}, T_{max} and $AUC_{(0-\infty)}$ of mini-tablets formula (FF9) when compared to the marketed product (Spasmocure® tablet). In addition, the relative bioavailability was 208.31 % based on the mean value of $AUC_{(0-\infty)}$ of the tested formula (FF9) compared to that of the reference standard product (Spasmocure® tablet). It might be concluded that the gastro-retentive extended release of drotaverine hydrochloride from floating mini-tablets formula (FF9) composed of sodium alginate 200 mg and sodium bicarbonate 120 mg for a period of 24 h resulted in retardation in drug absorption and higher bioavailability as evident by the significant delayed T_{max} and higher C_{max} and $AUC_{(0-\infty)}$.

5. Conclusion

A potential drotaverine hydrochloride gastroretentive system intended for once-daily oral administration was successfully developed. Floating mini-tablets formula (FF9) has more acceptable results that attributed to acceptable physiochemical properties of mini-tablets and optimum floating behavior (floating lag time 49.1 ± 5.3 s and total floating time > 24 h). It also exhibited significant ($p < 0.05$) prolonged

release for DRH (7.60 ± 1.25 % after 0.5 h and 78.14 ± 3.10 % after 12 h) when compared with marketed product Spasmocure® (90.22 % after 0.5 h). The improved bioavailability with prolonged plasma profile of DRH after oral administration of floating mini-tablets formula (FF9) compared to marketed tablet could be attributed to the floating behavior of mini-tablets that increase its residence time in the stomach which could provide prolonging DRH absorption rate. Consequently for FF9, less dosing frequency (once-daily) could be used. Therefore, the oral administration of drotaverine hydrochloride in the form of floating mini-tablets (FF9) could be a promising candidate for gastroretentive drug delivery system for DRH.

Declaration of competing interest

No conflict of interest.

Acknowledgment

Appendix A. Supplementary data

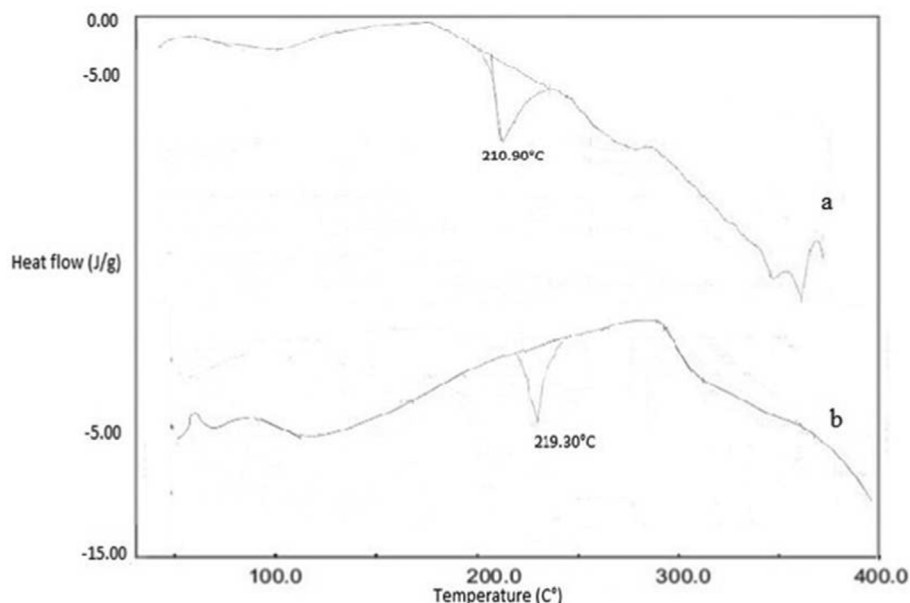Supplementary data to this article can be found online at https://

Fig. 3. DSC thermogram of (a) pure DRH and (b) DRH and excipients mixture.
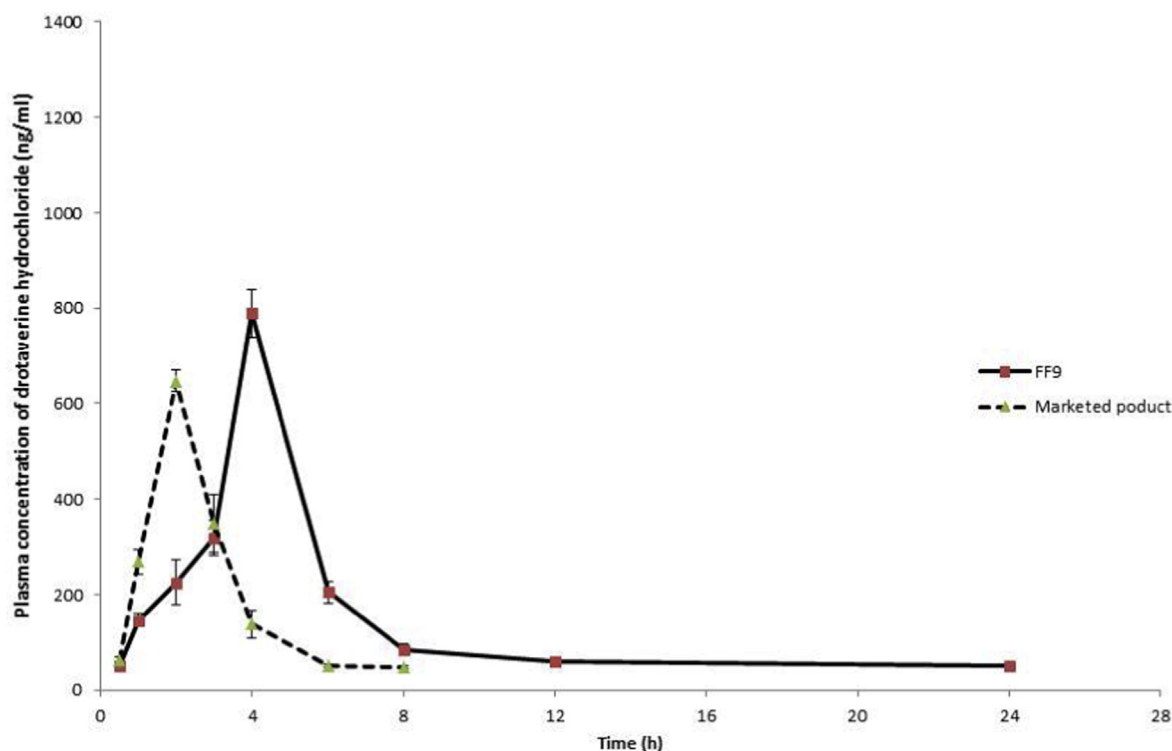
Fig. 4. Mean plasma concentration-time profiles of DRH following administration of floating mini tablets formula (FF9) and marketed product (Spasmocure® 60 mg).

Table 4
Mean pharmacokinetic parameters and relative bioavailability of DRH after administration of mini-tablets FF9 and marketed product.

Pharmacokinetic parameters	Mini-tablets FF9	Marketed product
Cmax (ng/ml)	788.32 ± 51.53	648.14 ± 23.53
Tmax (h)	4	2
AUC (0–24) (ng.hr/ml)	3298.92 ± 182.22	1589.06 ± 128.01
AUC (0-∞) (ng.hr/ml)	3311.31 ± 182.18	1589.54 ± 127.97
Frel (%)	208.31	–

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