RESEARCH ARTICLE

Design and *In Vitro* Evaluation of Gastroretentive Tablets of Doxylamine succinate

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Abstract

Aim: The aim of the study was to prepare and evaluate a gastroretentive sustained release delivery system for doxylamine succinate, using a release-retarding polymer. The floating approach was applied for preparing gastroretentive tablets (GRT). **Materials and Methods**: Four GRT formulations were prepared by melting granulation technique followed by double compression. The granules were subjected to pre-compression evaluation, namely, angle of repose, loose and tapped bulk densities, Carr's compressibility index, and Hausner's ratio. Three of the GRT formulations were prepared using hydroxypropyl methylcellulose K4M (HPMC K4M) as a release-retarding polymer, at different concentrations. **Results and Discussion**: The mechanism of doxylamine released from the GRT formulations were then assessed by fitting the *in vitro* dissolution data obtained to zero-order, first-order, Higuchi's, and Korsmeyer–Peppas models. It seems that formulations containing different concentrations of HPMCK4M, closely follow the first-order and Higuchi models for kinetic of drug release. Although the regression coefficients of zero-order and Korsmeyer–Peppas model for the three formulations showed relatively low values, all diffusion exponent (n) values, were above 0.5 value, which indicates that the mechanism of drug release from those formulations follow a non-Fickian release (diffusion and swelling) as expected from hydrophilic polymers like HPMC K4M. **Conclusion**: The use of a release-retarding polymer like HPMC K4M together with the floating-tablet technology can be applied to formulate basic drugs that have low solubility at the intestinal pH, to achieve sustained release pattern.

Key words: Doxylamine, gastroretentive tablet, hydroxypropyl methylcellulose, melt-granulation

INTRODUCTION

Gastroretentive drug delivery system is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. This drug delivery system not only prolongs GI residence time but also does so in an area of the GI tract that could maximize drug reaching its absorption site in solution, and hence, ready for absorption.[1-3] Gastroretentive system can remain in the gastric region for several hours, and hence, significantly prolong the gastric residence time of the drug in the GIT. Potential drug candidates for gastroretentive tablets (GRT) are drugs, which are locally active in the stomach, e.g. misoprostol and antacids primarily absorbed in the stomach, poorly soluble at an alkaline pH, e.g. basic drugs, having narrow absorption window in GIT such as L-dopa, and para-amino benzoic acid and drugs unstable in the intestinal or colonic environment such as captopril and metronidazole.[4] The gastric emptying time and the variation in pH in different segments of GIT are the major challenging task for the development of oral controlled release drug delivery system. Various attempts have been made to enhance the residence time of the dosage form within the stomach.[5-8] It has been suggested that prolonged local availability of antimicrobial agents in GIT may augment their effectiveness in treating H. pylori-related peptic ulcer.[9-11] GRT, however, are not suitable for drugs that may cause gastric irritation, e.g., nonsteroidal anti-inflammatory drugs, or drugs that are unstable in the acidic environment of the stomach.[11]

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GRT have a bulk density less than gastric fluids (<1.004 g/ml) and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.[12,13]

While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of the drug, the residual system is emptied from the stomach. This results in an increased gastric resident time and a better control of fluctuations in plasma drug concentration. The floating sustained release dosage forms possess most of the characteristics of hydrophilic matrices and are known as "hydrodynamically balanced systems" since they are able to maintain their low apparent density, while the polymer hydrates and builds a gelled barrier at the outer surface. The drug is released progressively from the swollen matrix, as in the case of hydrophilic matrices.[12]

Doxylamine succinate, IUPAC systematic name is pyridine, 2-[α-[2-(dimethylamino)ethoxy]-α-methylbenzyl]-, succinate (1:1), succinic acid, compound. Its molecular formula is $C_{17}H_{22}N_2O.C_4H_6O_4$, and the relative molecular mass is 388.46. It is white or creamy-white powder, melting-point: 100–104°C, very soluble in water (1 g/ml at 25°C) and chloroform; soluble in ethanol; slightly soluble in benzene and diethyl ether. The pKa of doxylamine are 5.8 and 9.3.[14] The US Pharmacopoeia specifies ultraviolet absorption spectrophotometry (ʎ = 262 nm); with a comparison to standards as the method for identifying doxylamine succinate; titration with perchloric acid is used to assay its purity. In pharmaceutical preparations, doxylamine succinate is identified by infrared absorption spectrophotometry; ultraviolet absorption spectrophotometry and high-performance liquid chromatography are used to assay for content.[15]

Doxylamine succinate, an ethanolamine-based antihistamine, shares the actions and uses of other antihistamines. Due to its sedative effect, it is used in the short-term management of insomnia. It is used for the symptomatic relief of hypersensitivity reactions and in the treatment of pruritic skin disorders. It is also used in combination with antitussives and decongestants (e.g., dextromethorphan, pseudoephedrine,and phenylpropanolamine)for the temporary relief of cough and cold symptoms.[16] Doxylamine succinate is commercially available as an over-the-counter 25 mg tablet and a 50 mg liquid-filled capsule; it is also available in combination with antitussives and decongestants. Doxylamine succinate is also used in over 50 pharmaceutical preparations in combination with other drugs.[17]

The usual oral dose of doxylamine succinate as an antihistamine for adults and children 12 years and older is 7.5–12.5 mg every 4–6 h, not to exceed 75 mg within 24 h. Under the direction of a physician, these patients may receive up to 25 mg every 4–6 h, not to exceed 150 mg within 24 h. The usual oral dose for children 6–12-year-old is 3.75–6.25 mg every 4–6 h, not to exceed 37.5 mg within 24 h. Under the direction of a physician, these pediatric patients may receive up to 12.5 mg every 4–6 h, not to exceed 75 mg within 24 h. Under the direction of a physician, children aged 2–<6 years may receive an antihistaminic dose of 1.9–3.125 mg every 4–6 h, not to exceed 18.75 mg in 24 h. The drug is contraindicated in neonates.[16]

MATERIALS AND METHODS

Materials

Doxylamine succinate, hydroxypropyl methylcellulose K4M (HPMC K4M) and magnesium stearate were purchased from Sigma Pharmaceuticals, sodium bicarbonate was purchased from Sharlu (Spain) beeswax was purchased from Euro, lactose was purchased from Loba Chemie PVT, and talc was purchased from Riedel de Haen.

Methods

Dose calculation

For sustained drug release up to 12 h, the total dose of drug required was calculated based on the fact that the conventional dose of doxylamine succinate tablets, as an antihistamine is 10 mg. The total dose was calculated using the following equation:

$$D_t = \text{Dose}\ (1 + 0.693 \times t/t_{1/2})$$

Where, D_t = Total dose, Dose = Immediate release dose, t = Total time period for which sustained release is required, $t_{1/2}$= Half-life of drug.

For doxylamine succinate:

$D_t = 10[1+(0.693\times12)/10)]=18.3$ mg (approximated to 18.5 mg).

Preparation of GRT by melt granulation and double compression technique

All the four formulations shown in Table 1, were prepared in the same way. The required amount of beeswax was transferred to a porcelain dish over a water bath for melting the wax.

Table 1: Formulation

Ingredients (in mg)	F1	F2	F3	F4
Doxylamine succinate	18.5	18.5	18.5	18.5
HPMC K4M	0	75	100	150
Sodium bicarbonate	65	65	65	65
Beeswax	75	75	75	75
Lactose	311.5	236.5	211.5	161.5
Magnesium stearate	15	15	15	15
Talc	15	15	15	15
Total tablet weight	500	500	500	500

HPMC K4M: Hydroxypropyl methylcellulose K4M

Doxylamine succinate was then added to the molten mass and mixed well. The previously prepared geometric mixture of HPMC K4M, sodium bicarbonate, lactose was added to the molten mass and stirred well to through mix. Then, the coherent mass was removed from the water bath and was scrapped until it attained room temperature. The coherent mass was then passed through sieve no. 24. The granules were collected and mixed with talc and magnesium stearate. The lubricated blend was then compressed into tablets using 12 mm standard concave punch with an automatic single punch Erweka machine (Type EPI). The tablets are then granulated using the Erweka dry granulator. T (Type TG2/S). The resultant granules are then recompressed into the final tablets using 12 mm standard concave punch with an automatic single punch Erweka machine (Type EPI).

Evaluation of granules

The flow property of the granules was evaluated by determining Carr's compressibility index, Hausner ratio and the angle of repose.

Bulk density

Loose bulk density (LBD) and tapped bulk density (TBD) were determined for the prepared granules. LBD and TBD were calculated using the formulae:

LBD = Weight of powder/volume of powder.

TBD = Weight of powder/tapped volume of powder.

Carr's compressibility index and Hausner ratio

Carr's compressibility index for the prepared granules was determined by the equation:

Carr's compressibility index (%) = TBD–LBD/TBD×100

Hausner ratio = TBD/LBD

Angle of repose

The static angle of repose was measured according to the fixed funnel method. The angle of repose was calculated using the equation:

Tan θ = h/r where, θ is the angle of repose.

Evaluation of tablets

Physicochemical properties

Tablets from all the four formulations were evaluated for various physicochemical properties including weight variation using an electronic balance (Chaus Citizen), thickness using Vernier caliper, hardness using Monsanto hardness tester (Erweka) and friability using Erweka Friabilator.

In vitro buoyancy studies

In vitro buoyancy was determined by floating lag time as per the method described by Rosa *et al*. The tablets were placed in a 100 ml glass beaker containing 0.1 M HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time. In addition, the total floating time was also determined.

In vitro dissolution studies

The *in vitro* dissolution study of doxylamine succinate tablets was performed using USP XXII Dissolution test apparatus employing paddle stirrer (75 rpm) at 37 ± 0.5°C using simulated 0.1 M HCl (900 ml) as a dissolution media. At the predetermined time intervals, 5 ml samples were withdrawn, diluted, and assayed at m = 264 nm using a Beckman DU 730 spectrophotometer. The cumulative percentage drug release was calculated from the calibration curve constructed using doxylamine succinate reference sample.

Release kinetics analysis

The drug release data were fitted to various models, namely; Higuchi's model (cumulative percent release against square root of time), zero-order model (cumulative percent release against time), first-order model (log cumulative percent remaining to be released against time), and Korsmeyer's–Peppas model (log cumulative percent release against log time) to assess the release kinetics and identify the release mechanism.

RESULTS AND DISCUSSION

All four formulations showed good flow properties, as shown in Table 2. The LBD and tapped density ranged from 0.372 to 0.556 and 0.397 to –0.594, respectively. Carr's compressibility index ranged from 3.64% to 9.77%, and Hausner ratio ranged from 1.04% to 1.11%. The angle of repose ranged from 27°.75' to 31°.49'.

These results indicate that the prepared granules exhibit good flow property needed to achieve ideal tablet compression.

The shape of the tablets of all four formulations remained circular with no visible cracks. The weight variation of 20

Table 2: Evaluations of the granules

0.28	LBD (g/ml)	TBD (g/ml)	Carr's index (%)	Hausner ratio	Angle of repose (0)
F1	0.536	0.594	9.77	1.11	31.49
F2	0.556	0.577	3.64	1.04	30.47
F3	0.484	0.518	6.56	1.07	27.75
F4	0.372	0.397	6.30	1.07	30.10

tablets ranged from ±1.03% to ±1.61% (below 5%), the thickness ranged from 4.17 ± 0.04 mm to 4.45 ± 0.04 mm, complying with pharmacopeia specifications. The hardness of the tablets ranged from 1.72 ± 0.21 to 2.84 ± 0.55 indicating a satisfactory mechanical strength. The percentage friability of the four batches ranged from 0.02% to 0.14% (below 1%) complying with pharmacopeia specifications [Table 3].

In vitro buoyancy studies

All four formulations exhibited satisfactory floatation ability and remained buoyant for more than 24 h in dissolution medium (0.1 M HCl). The buoyancy lag time of formulation F1 was strikingly more than 6 h, and since this formulation does not contain any HPMC, this observation could indicate that HPMC may have a role in the floating action of such tablets. The main floating action is attributed to sodium bicarbonate that interacts with the acidic media leading to CO_2 evolution that promotes floating. In addition, the oily nature of beeswax may contribute to the floating action, since oils have lesser density than water. Formulations F2, F3, and F4 showed buoyancy lag times ranging from 80 to 180 s [Table 4]. These results indicate that the buoyancy lag time, for these three formulations, was satisfactory.

In vitro dissolution studies

The *in vitro* drug release studies revealed that 96.60% of formulation F1 has been released within the first 7 h. This was expected, as this formulation does not contain any HPMC K4M that acts as release-retarding polymer. Formulations F2, F3, and F4 show release of 92.00%, 88.60%, and 87.31%, respectively, at the end of 12 h. These data revealed that the three formulations show sustained release pattern [Table 5 and Figure 1], with formulation F3 showing a superior buoyancy lag time of 80 s [Table 4].

Drug release kinetics

Formulations F2, F3, and F4 were then analyzed for their drug release kinetics as well as their mechanism of drug release. The data obtained from *in vitro* release studies [Table 5] were subjected to zero-order model [Table 6 and Figure 2], first-order model [Table 6 and Figure 3], and Higuchi's model [Table 6 and Figure 4] to assess their release kinetics. Whereas the mechanism of drug release was tested by Korsmeyer's models [Table 6 and Figure 5].

From the regression coefficient values [Table 7], it seems that formulations F2, F3, and F4, containing different concentrations of HPMC K4M, closely follow the first-order and Higuchi models for kinetic of drug release. Although the regression coefficients of zero-order and Korsmeyer–Peppas model for the three formulations showed relatively low values, all diffusion exponent (n) values, were above 0.5 value, which

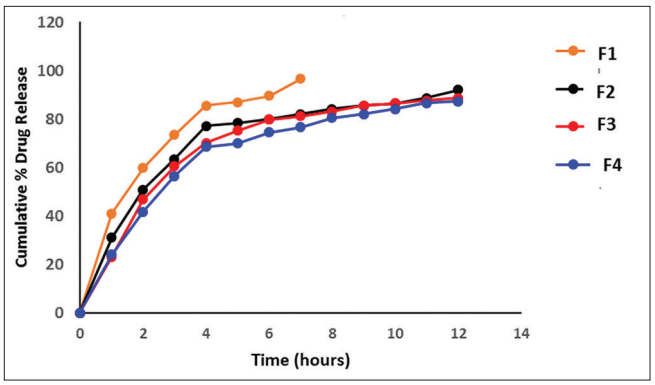

Figure 1: *In vitro* dissolution release profiles for formulations F2, F3, and F3

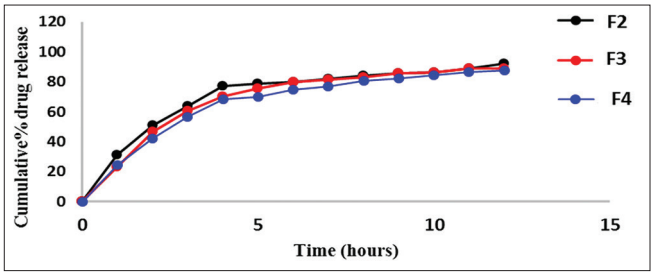

Figure 2: Zero-order kinetic release model for formulations F2, F3, and F4

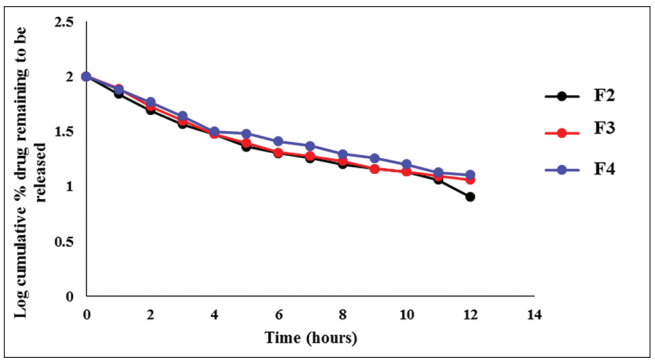

Figure 3: First-order kinetic release model for formulations F2, F3, and F4

Table 3: Evaluations of physicochemical properties of doxylamine succinate GRT

Batch. No	Weight Variation mg (±% SD)	Thickness (mm)	Hardness (Kg/cm²)	Friability (%)
F1	502.9±1.53	4.17±0.04	2.15±0.58	0.14
F2	502.7±1.47	4.30±0.04	2.84±0.55	0.02
F3	496.8±1.61	4.45±0.04	1.84±0.28	0.10
F4	503.6±1.03	4.39±0.05	1.72±0.21	0.10

SD: Standard deviation, GRT: Gastroretentive tablets

indicates that the mechanism of drug release from the three formulations follow a non-Fickian release (diffusion and swelling) as expected from hydrophilic polymers like HPMC K4M.[18,19] However, increasing the concentration of HPMC K4M that acts as a release-retarding polymer did not clearly affect the release rates of all three formulations (F2, F3, and F4) which exhibited almost similar release patterns [Table 5 and Figure 1].

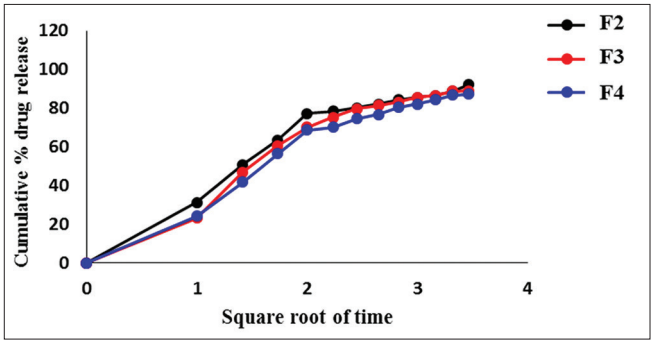

Figure 4: Higuchi kinetic release model for formulations F2, F3, and F4

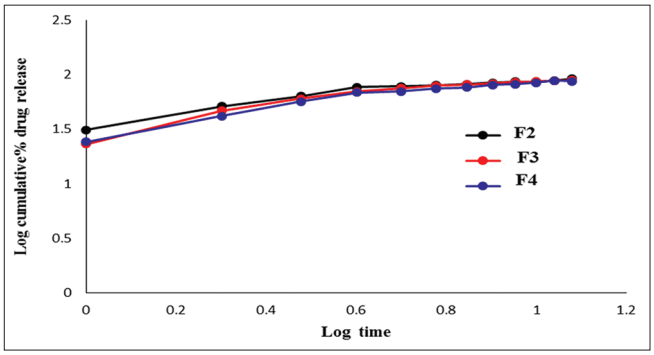

Figure 5: Korsmeyer–peppas kinetic release model for formulations F2, F3, and F4

Table 4: Buoyancy lag time and total floating time

Batch. No	Buoyancy lag time (s)	Total buoyancy time (h)
F1	21600	>24
F2	160	>24
F3	80	>24
F4	180	>24

Table 5: *In vitro* release profile

Time (h)	Cumulative drug release (%)			
	F1	F2	F3	F4
1	41.13	31.13	23.13	24.13
2	59.80	50.80	46.80	41.80
3	73.43	63.43	60.43	56.43
4	85.50	77.10	70.10	68.50
5	87.00	78.40	75.20	70.00
6	89.50	80.00	79.70	74.50
7	96.60	82.05	81.23	76.60
8		84.20	83.11	80.40
9		85.60	85.60	82.05
10		86.4	86.40	84.20
11		88.6	87.60	86.60
12		92.00	88.60	87.31

All dissolution data are the mean of two values

Table 6: Drug release kinetics of formulations F2, F3, and F4

Time (h)	Cumulative% drug release			Log cumulative% drug remaining to be released			Square root of time	Log cumulative% drug release			Log time
	F2	F3	F4	F2	F3	F4		F2	F3	F4	
0	0	0	0	2.000	2.000	2.000	0	0	0	0	0
1	31.13	23.13	24.13	1.838	1.886	1.880	1	1.493	1.364	1.383	0
2	50.80	46.80	41.80	1.692	1.726	1.765	1.414	1.709	1.670	1.621	0.301
3	63.43	60.43	56.43	1.563	1.597	1.639	1.732	1.802	1.781	1.752	0.477
4	77.10	70.10	68.50	1.476	1.476	1.498	2.000	1.887	1.846	1.836	0.602
5	78.40	75.20	70.00	1.360	1.394	1.477	2.236	1.894	1.876	1.845	0.699
6	80.00	79.70	74.50	1.300	1.307	1.407	2.449	1.903	1.901	1.872	0.778
7	82.05	81.23	76.60	1.254	1.273	1.369	2.646	1.914	1.910	1.884	0.845
8	84.20	83.11	80.40	1.199	1.228	1.292	2.828	1.925	1.920	1.905	0.903
9	85.60	85.60	82.05	1.158	1.158	1.254	3.000	1.935	1.932	1.914	0.954
10	86.4	86.40	84.20	1.134	1.134	1.199	3.162	1.937	1.937	1.925	1.000
11	88.6	88.60	86.60	1.057	1.093	1.127	3.317	1.947	1.947	1.947	1.041
12	92.00	88.90	87.31	0.903	1.057	1.103	3.464	1.964	1.949	1.941	1.079

Table 7: Regression coefficient (R^2) values of formulations F2, F3, and F4

Formulation	Zero-order	First-order	Higuchi	Korsmeyer–Peppas	
	R^2	R^2	R^2	R^2	Diffusion exponent (n)
F2	0.8460	0.9749	0.9561	0.7166	0.6545
F3	0.8692	0.9661	0.9649	0.7536	0.8607
F4	0.8888	0.9784	0.9750	0.7563	0.7534

CONCLUSION

Formulations F2, F3, and F4 containing different concentrations of HPMC K4M, show sustained release patterns for up to 12 h and exhibit good buoyancy and total floating times. Increasing the concentration of HPMC K4M that acts as a release-retarding polymer did not clearly affect the release rates of all three formulations (F2, F3, and F4), which exhibited almost similar release patterns. GRT with sustained release characteristics offer critical advantages such as site specificity with improved absorption and efficacy. The use of a release-retarding polymer like HPMC K4M together with the floating-tablet technology can be applied to formulate basic drugs that have low solubility at the intestinal pH, to achieve sustained release pattern. In addition, drugs that are mainly absorbed from the stomach are also good candidates for such technology. Moreover, floating mechanism does not require any complex technology, and hence, easy to adopt which is considered a clear advantage.

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