

PREPARATION AND *IN-VITRO* EVALUATION OF DESLORATADINE FLOATING TABLETS

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ABSTRACT

Objective: Desloratadine is histamine H₁ - receptor antagonist used in treatment of allergic and rhinitis conditions. The tablets were prepared by direct compression technique, using polymers such as Carbopol 934P, Carbopol 940P either alone or combination and other excipients such as NaHCO₃, citric acid, mannitol, avicel pH 102, SDL.

Methods: The prepared tablets were evaluated in terms of their physical properties, hardness, % friability, weight variation, content uniformity, drug-excipient compatibility (FTIR), in-vitro release, floating properties and swelling index. Result shows that as amount of carbopol 934P increased the drug release decreased due to increase penetration of water in to polymer. It was found that increase sodium bicarbonate concentration cause an increase in the floating time (FLT) were also increased drug release while floating time was decreased due to decrease in matrix coherent.

Mannitol showed the best release properties as a diluent when compared with Avicel pH 102 and SDL the drug release was accelerated.

Results: Swelling index studies of selected formula (F9) 96% compared with other formulas gave rapid release of desloratadine that indicated a combined effect of both diffusion and erosion mechanisms on drug release from floating dosage form.

Conclusion: The stability of the selected formula (9) was also studied at different temperatures (40, 50 and 60°C) for three months and the calculated shelf life data was found to be about 2.7 years.

Keywords: Desloratadine, Effervescent floating tablets, Carbopol 934P, NaHCO₃, Citric acid.

INTRODUCTION

The oral route is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery has recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dose administration, patient compliance and flexibility in formulation[1].

The effective oral drug delivery, may depend up on many factors such as gastric emptying process, gastro intestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs. Most of the oral dosage forms possess several physiological limitation such as variable gastro intestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, in complete drug release and shorter residence time of dosage form in the stomach. This lead to incomplete absorption of drugs having window absorption especially in the upper part of small intestine, as once the drug possess down the absorption site, the remaining quantity goes unabsorbed. The gastric emptying of dosage forms in humans is affected by several factors. Because of which wide inter- and intra- subject variation are observed[2].

Since many drugs as well absorbed in the upper part of the gastro intestinal tract, such high variability may lead to non-uniform absorption and makes the bioavailability unpredictable. Hence a beneficial delivery system would by one which processes the ability to prolong the gastric time and can deliver drugs in higher concentrations to the absorption site (i. e. Upper part of the small intestine). The identification of new diseases and the resistance shown towards the existing drugs called for the introduction of new therapeutic molecules. In response, along number of chemical entities have been introduced, of which some have absorption all over the gastro intestine tract (GIT), some have window absorption (i.e. Absorption sites, especially the upper part of the small intestine) and some drugs have poor solubility intestinal media. The drugs belonging to the second and third categories, and the drugs which are required for local action in the stomach, require a specialized

delivery system[3]. The oral route is increasingly being used for the delivery of the therapeutic agent because of the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery system available in the market are oral drug delivery systems[4].

Floating dosage form is most acceptable route for drug administration. As conventional dosage forms several other forms were developed in order to enhance the drug delivery for prolonged time period and for delivering drug to a particular target site. After the drug release for required time period, the dosage form should get degraded without causing any gastric disturbances[5]. Desloratadine is non-sedating antihistamine with chemical name 8-chloro-6, 11-dihydro-11- (4-piperdiny lidene-5H-benzo [5, 6] cyclohepta [1, 2-b] pyridine). It is used for the treatment of asthma and allergic rhinitis. It is an oral, long-acting anti histaminic drug, which is chemically similar to loratadine. It is used to treat the symptoms caused by the release of histamine[6]. Histamine is a chemical that is responsible for many of the signs and symptoms of allergic reactions, so desloratadine can be used for the treatment of allergic asthma and allergic rhinitis conditions [7].

MATERIALS AND METHODS

Materials

Desloratadine, (gifted by Hawler University, college of pharmacy Iraq), Carbopol 934P, sodium bicarbonate, and citric acid, (Samara drug industries (SDI), Iraq).

Method

Formulation of desloratadin floating tablet

Different formulas of *desloratadin* floating tablets were prepared as shown in table (1). They were prepared using direct compression method. They previously weighted ingredients were homogenously mixed in a mortar for fifteen minutes in order to obtained a homogenous mixture of powder blend, a known weight of the powders blend of different ingredients were mixed with a calculated amount of

magnesium stearate and talc powder for five minutes and then

compressed using 9 mm biconcave punch tableting machine [8].

Table 1: Composition of the float tablets using different ingredients types and concentrations

Formula No.	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Ingredients (mg)													
Desloratadine	5	5	5	5	5	5	5	5	5	5	5	5	5
Carbopol 934P	60	70	80	-	30	60	60	60	60	60	60	60	60
Carbopol 940P	-	-	-	60	30	-	-	-	-	-	-	-	-
Sodium bicarbonate	36	36	36	36	36	30	-	18	36	36	36	36	36
Calcium carbonate	-	-	-	-	-	-	36	18	-	-	-	-	-
Citric acid	18	18	18	18	18	18	18	18	18	18	18	18	18
PVP K30	6	6	6	6	6	6	6	6	6	6	6	6	6
Mg stearate	6	6	6	6	6	6	6	6	6	6	6	6	6
Talc	3	3	3	3	3	3	3	3	3	3	3	3	3
Avicel pH102 (MCC)	66	56	46	66	66	72	66	66	-	-	33	33	-
Mannitol	-	-	-	-	-	-	-	-	66	-	33	-	33
Spray dried lactose (SDL)	-	-	-	-	-	-	-	-	-	66	-	33	33
Total weight (mg)	200	200	200	200	200	200	200	200	200	200	200	200	200

Evaluation of the prepared floating tables:

Weight variation

The weight variation of the prepared floating tablet was done by weighting twenty tablets individually and the average weight was calculated. For the tablets to be accepted, the weight of not more than two tablets deviates from the average weight by no more than 7.5% and no tablet deviates by more than 15% [9].

Hardness

The hardness (force required to break a tablet by diametrical compression) of all the prepared floating tablets (with and without Desloratadine). The test was done using manual Monsanto hardness tester in which the hardness was measured in terms of kg/cm². Since the minimum practical hardness that provide adequate mechanical resistance is not less than 3 Kg/cm²[10].

Friability

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm for 4 min and dropping a tablet at height of 6 inches in each revolution.

Pre weighted sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed.

The following equation was used to calculate the percentage friability of tablet:

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

The percentage of friability of tablets should not exceed 1% (w/w) of total weight of tablets to be accepted[11].

Content uniformity

This test was done for each formula that loaded with Desloratadine. The test was done, protected from light, tablet was dissolved in 100 ml of distilled water and the absorbance of the final solution was measured at the maximum at 282 nm.

This test is used to determine whether the individual contents are within limits set with references to the average contents of the sample. The preparation complies with the test if each individual content is 85 to 115 per cent of the average content[12].

In-vitro buoyance studies

The *in vitro* buoyancy was determined by floating lag time (FLT) and total floating time (TFT) as the method described by Rosa et al. the tablets were placed in 100 ml beaker containing 0.1N HCL. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and the duration of the time

the tablet constantly floats on the dissolution media was noted as the total floating as the total floating time respectively (TFT) [13].

Swelling index

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in 100 ml beaker of 0.1NHCL and after 1,2,3,4 and 5 hrs. each, beaker containing tablet with drawn, blotted with tissue paper to remove the excess water and weight on the analytical balance. The swelling index (SI), expressed as a percentage, and was calculated from the following equation[14].

$$SI = \frac{\text{weight of tablets at time (t)} - \text{Initial weight of tablet}}{\text{Initial weight of tablet}} \times 100$$

Drug release

Effect of polymer concentration

Formula 1, 2 and 3 were prepared to study the effect of polymer amount on the floating properties and to determine the amount of polymer that is enough to controlled the drug release. Different amount of carbopol 934P 60 mg, 70 mg and 80 mg respectively were used in these formulas.

Effect of polymer type and combination

Formula (4) which contain carbopol 940P was used to study the effect of polymer type and its concentration on the floating and drug release properties. F5 was prepared to study the effect of combination of carbopol 934P and carbopol 940P at 15% w/w concentration of each on the drug release and floating properties.

Effect of types of diluent

Formulas (1-8) which contain avicel pH 102 (MCC) as a diluent was used to study the effect of changing type of diluents on the drug release and floating behavior; MCC was replaced by spray dried lactose (SDL) in formula 10 and mannitol in formula 9.

Effect of diluent combination

Formula 11 was prepared to study the effect of combination of (MCC and mannitol), F12 (MCC+SDL) and F13 (SDL+mannitol) at 16.5% w/w concentration for each diluent, so that the final percent for each combination is 33% w/w of the formula on the drug release and floating properties.

Drug-excipients compatibility studies

Fourier transform infrared (ftir) spectroscopic

Drug-excipient interaction is one of the most important compatibility studies, FTIR study was used for this purpose on samples of pure desloratadine and blend powder of F9. Spectra were

obtained using (Shimadzu 8300, Japan) according to KBr disk method.

About 2-3 mg sample were mixed with dried IR grade potassium bromide powder and the spectra were in between the wave number range of 4000-400 cm^{-1} [15].

Stability studies

Effect of storage temperatures (determination of shelf life)

The effect of temperature on the degradation of desloratadine, the selected optimum F9 was studied. They study was done by storing the tablets in ovens at different temperatures of (40, 50 and 60) $^{\circ}\text{C}$, for three months. Samples were withdrawn at certain time intervals to determine the content of desloratadine. By measuring their UV absorbance at its λ_{max} . The content of desloratadine was measured by HPLC analysis method.

RESULTS AND DISCUSSION

Evaluation of desloratadine floating tablets

Weight variation

The weight variation of floating tablets as shown in table (2), it was found in rang (0.49%-1.47%)to all formulations. This result fulfills the USP requirements in the limits +7.5% of the average weight (the USP specification is generally +7.5% for tablet weighting 130 to 324mg)[16]. That means no difference was observed in the weight of individual tablet from the labeled to weight indicating uniformity of weight.

Hardness

The measured hardness of all formulas as shown table (2). The hardness was in range of 7.5 to 9.7kg/cm² in all formulation indicated good mechanical strength with physical and mechanical stress condition, this may be referred to increasing the concentration of carbopol that present in formulas, tablet hardness was significantly increased with increased polymer concentration, viscosity and compression force[17]. This was attributed to the carbopol polymer as thickening agents and tablets compressed matrix forming agents[18].

Friability

The loss in total weight of the tablets due to friability is in the range of 0.12% to 0.77% in all formulation and the friability value is less than 1% which ensure that formulated tablets are mechanically stable; friability was unaffected with polymer concentration and viscosity, however was significantly decreased with increased compression force[17]. This was attributed to the floating matrix tablets containing high amount of carbopol showed higher bioadhesion time and bonding than that of the lesser amount[19].

Content uniformity

The content uniformity of the prepared desloratadine floating tablets (table 2) showed that all formulas of desloratadine prepared floating tablets with accept limit of content uniformity. No tablets lie out of the range of (85-115)% of the label claim. These results indicated that the prepared dosage form (floating tablets) had uniform distribution and proper dose of the active ingredient, which may be attributed to the effect of carbopol excellent mucoadhesive strength and controlled drug release[20].

Determination of the floating lag time (flt) and total floating time (tft)

All the tablets were prepared by effervescent method; the results are shown in (table 3). Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced CO₂ generation in presence of dissolution media (0.1NHCL), and it was observed that the gas generated is trapped and protected with in the gel, formed by hydration of polymer (carbopol 934P).

Most of batches of tablets were found to exhibit short FLT due to the presence of sodium bicarbonate, increasing the carbopol 934P level in formulas prolonged the FLT and TFT as shown in formulas (1,2 and 3) which they have a lag time values of 16, 20 and 22 sec. and TFT of 9, 8 and 7.5 hrs., respectively. This can be explained by that a high polymer content result in the formulation of a strong gel, as a carbopol 934P content is increased, the resulting gelatinous diffusion layer becomes stronger and more resistant to diffusion[21].

Tablets of batches containing carbopol 940P, F(4 and 5) gave a high FLT (15 and 20 sec.) and allow TFT (8 and 6 hrs.) due to carbopol 940P which has a negative on the effect on the floating behavior of the delivery system and this can be explained by that carbopol 940P has a much a higher moisture absorption, result in a dramatic increase in the density of the FDDS, shows a corresponding decrease in the floating of FDDS[22].

Furthermore, the addition of calcium carbonate instead of sodium bicarbonate in formula 7, which they has a lag time (25 sec.) and TFT value of 22 hrs. because of calcium carbonate insoluble in water and its hydrophobicity might be duration of floating for the tablets [23].

Determination of the swelling index of the floating tablets

The swelling index of all formulas as prepared as shown in (Table 3). Among, all formulations the F9 shows the best result of swelling index whereas the batch F8 showed the least value of the swelling index. The values of swelling index of the different batches ranged from 51.5% to 96.0%.

Table 2: Parameters of desloratadine floating tablets

Formula No.	Hardness (kg/cm ²)	Friability (w/w)	Desloratadine Content (%)	Weight Variation (%)
F1	9.7	0.26	99.0	0.5
F2	9.5	0.13	99.4	0.49
F3	8.5	0.27	97.6	0.49
F4	9.1	0.25	96.2	0.99
F5	9.0	0.25	99.1	0.94
F6	8.5	0.64	99.1	0.5
F7	8.0	0.77	99.2	0.5
F8	9.7	0.12	97.1	0.49
F9	7.5	0.50	99.7	0.99
F10	8.5	0.53	96.8	0.49
F11	8.5	0.38	98.0	0.99
F12	9.5	0.12	98.8	0.99
F13	9.0	0.26	98.1	0.5

The effect of polymer concentration

Formula 1, 2 and 3 were prepared to study the effect of carbopol 934P amount on the release profile of desloratadine, and it was found that as the amount of carbopol 934P increase the drug release

decrease and this indicates an inverse proportion between the drug release and the polymer to drug ratio (as shown in Figure 1)

This may be due to increased penetration of water into polymer. Similarly increase the swelling of carbopol which holds the water

inside the matrix and thus decrease the release of drug from the dosage form. This shows that carbopol 934P represents negative trends towards floating duration which is not desirable in floating drug delivery system[24]. Carbopol 934P might be higher affinity to water produce layer over tablets, which prevent dissolution of drug[25]. Non dissolved drug is not available for diffusion, while in the case of high initial drug loadings, the inner structure of the matrix changes significantly during drug release, becoming more porous and less restrictive for diffusion upon drug depletion[26].

Table 3: The floating capacity and swelling index of the prepared desloratadine floating tablets

Formula No.	Floating Lag Time FLT (seconds)	Total Floating Time TFT (hours)	Swelling Index(%)
F1	16	9	84
F2	20	8	93
F3	22	7.5	56.7
F4	15	8	55.8
F5	20	6	81
F6	27	6	63
F7	25	22	61
F8	9	20	51.5
F9	10	23	96
F10	10	16.5	69
F11	18	7	54
F12	6	21	71.4
F13	14	6.5	73

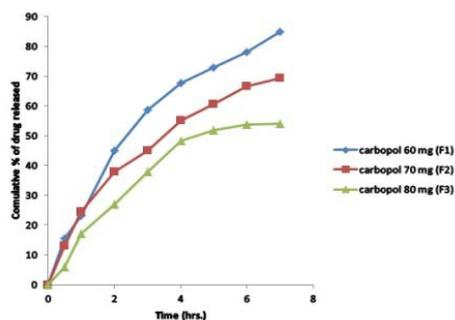


Fig. 1: The effect of carbopol 934P concentration on cumulative release of desloratadine from different formulas in 0.1N HCL at 37°C.

The Effect of Polymer Type and Combination

Formula 4 was prepared to study the effect of carbopol 940P on the release profile of desloratadine, the dissolution result shows that slower release is achieved with higher viscosity grade of carbopol 940P polymer in the formulation when compared with carbopol 934P (F1) at same concentration. This is mainly due to longer period of time required to reach the disentanglement concentration at the tablet surface, while in turn equates to greater resistance to surface erosion and also high viscosity polymer created more viscous gel layers, thus causing the drug to diffuse more slowly[27].

Formula 5 which containing carbopol 934P and carbopol 940P showed decrease in the rate of desloratadine release compared to use carbopol 934P (F1) or carbopol 940P (F4) alone. Because of higher viscosity of carbopol polymer, at a higher polymer loading, the viscosity of the gel matrix is increased which results in a decrease in the effective diffusion coefficient of the drug and hence decrease drug release into the dissolution medium[28] (as shown in Figure 2).

Effect of type of diluents

Several formulas which contain avicel 102 (MCC) as a diluent was used to study the effect of diluent type on desloratadine floating

tablets release profile, by changing the type of diluent from MCC to spray dried lactose (SDL) in formula 10 decrease rate of desloratadine release. This may be due to SDL its increased aqueous solubility and increased in rate of swelling of polymer in peripheral layer which in turn form a gelled matrix to control the release[29].

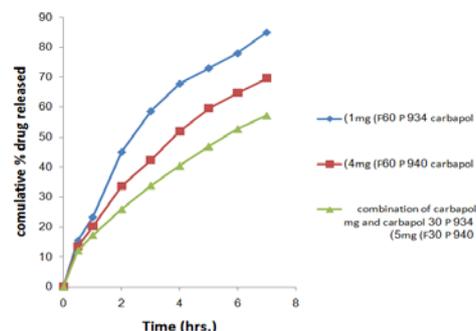


Fig. 2: The effect of carbopol type mixing on the cumulative release of desloratadine from floating matrix tablets in pH 1.2 at 37°C.

Lactose is well known water soluble filler, so incorporation of lactose leads to increase in hydration rate and relaxation of the polymer chains, resulting in more dissolved drug diffusion out from the matrix[30], by changing of MCC to mannitol in formula 9 increase in the rate of desloratadine release due to mannitol was selected as a diluent considering its advantages in terms of easy availability and negative heat of dissolution, it is water-soluble, non-hygroscopic, and produces a semi-sweet, smooth and cool taste. Because of its low hygroscopicity, mannitol is potentially an excellent excipient since it is compatible with the majority of active pharmaceutical ingredients[31]. (shown in Figure3)

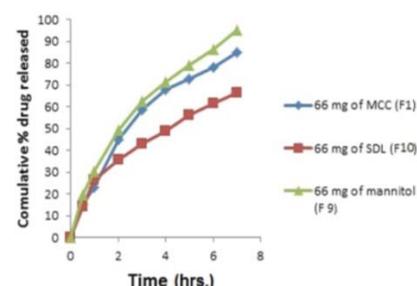


Fig. 3: The effect of diluent types on desloratadine cumulative release from floating matrix tablets in pH 1.2 at 37°C.

Effect of types of diluent combination

Formula 11 which contain avicel 102 (MCC) and mannitol showed decrease the rate of desloratadine release when compared with MCC alone or mannitol alone due to avicel was rapid passage of water into tablets resulting in the instantaneous rupture of the hydrogen bonds and rapid dis integration of tablets[32], while F12 contain MCC and spray dried lactose (SDL) showed decrease in rate of drug release than used for MCC or SDL alone because of SDL tends usually to dissolve rather than disintegrate, forming a viscous layer on the surface of the tablet which penetration of water into the tablet core[33].

Formula 13 which contain SDL and mannitol showed higher in the rate of desloratadine release than F11 and F12 that contain avicel. This may be due to contain combination of mannitol-lactose were used as Osmotic agents. This system was developed in two stage: formulation of core tablet and coating of tablet core. Core tablets

were evaluated for content uniformity, hardness and weight variation while coated tablets were evaluated for film thickness and in vitro release study[34]. (as shown in Figure 4)

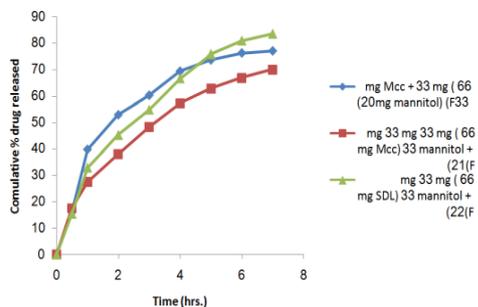


Fig. 4: The effect of combined diluents on desloratadine cumulative release from matrix tablets in pH 1.2 at 37°C.

Fourier transform infrared (ftir)

The interaction study between desloratadine and excipients in formulations were performed using FTIR spectrophotometer. The pellets were prepared on KBr press was introduced into FTIR spectra. The spectra were recorded over the wave number range of 4000 to 400 cm⁻¹. The major IR peaks observed in desloratadine were 3325.64 (3300-3400) (N-H) stretching of 2°-amine, 1705.73 (1665-2000) C=C, 727.11 (600-800) cm⁻¹ C-CL stretching in benzene ring (Figure 5). FTIR spectrum of desloratadine with physical mixture (F9), IR spectrum observed in matrices were 3327.57 (N-H) stretching of 2°-amine, 1710.48 (C=C), 725.25 cm⁻¹ (C-CL), hence it can be concluded that there was no interaction between drug and excipients, since similar peaks of specific functional groups were observed as shown in figure (6)

Stability effect of temperature (determination of expiration data)

The stability of the prepared desloratadine floating tablets (F9) was studied at three temperatures (40, 50 and 60°C). The degradation profile follows first order kinetics since a straight line was obtained when plotting the logarithm of percent drug remains versus time (figure 7). The degradation rate constant (k) can be calculated from the slope of the line; the results are shown in table (4).

Table 4: Degradation rate constant (k) of desloratadine floating tablets using formula (F9) at different temperatures

Temperatures (°C)	K (month) ⁻¹
40	4.67 × 10 ⁻³
50	6.02 × 10 ⁻³
60	7.41 × 10 ⁻³

In order to determine the expiration data (t_{10%}), Arrhenius plot was constructed to predict the degradation rate constant at 25°C (K₂₅) as shown in (Figure 8)

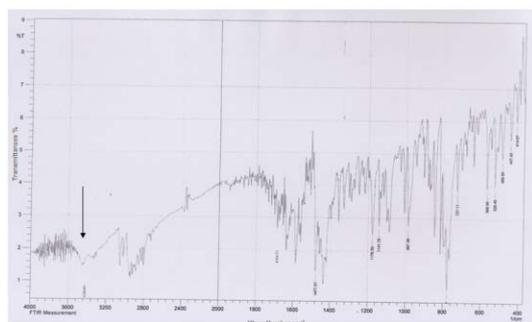


Fig. 5: FTIR Spectra of Desloratadine Pure Powder

The accelerated expiration data can be calculated using the following equation since the degradation of the drug follows first order kinetics[35]:

$$t_{10\%} = \frac{0.105}{3.23 \times 10^{-3}}$$

Where t_{10%} is the time required for a drug to lose t_{10%} of its potency and it was found to be (32.50) month or about (2.70) years for desloratadine floating tablets.

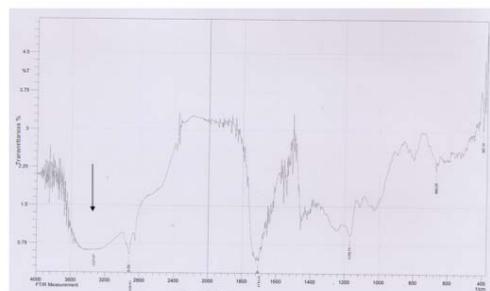


Fig. 6: FTIR Spectra of Desloratadine with Physical Mixture F9

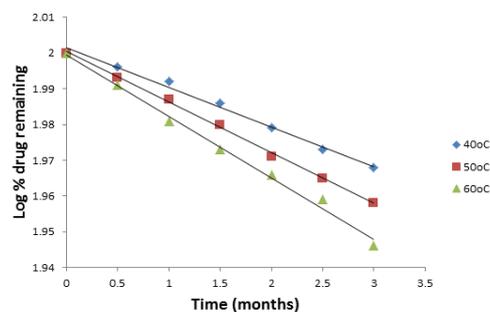


Fig. 7: Accelerated degradation of desloratadine in F9 at different temperature (40, 50 and 60°C).

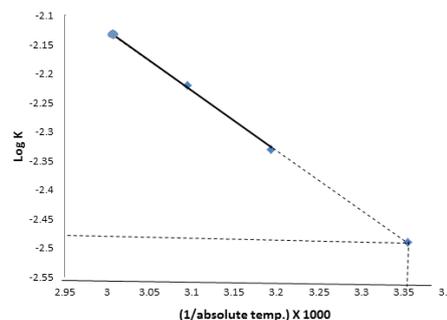


Fig. 8: Arrhenius plot of desloratadine in F9 for estimation of degradation constant (K₂₅°C).

CONCLUSION

Desloratadine was successfully formulated as controlled release floating tablet with a dose 5mg that extends the drug release for 24 hrs. This dosage form was prepared using effervescent technique by direct compression method.

Based on results, one can conclude the following points:

- 1- Increasing carbopol 934P concentration decreased the drug release from floating tablets, and increased the FLT and TFT.
- 2- Carbopol 940P had a negative effect on floating and decreased in FLT while increased in TFT.

3- Decreasing amount of sodium bicarbonate increased TFT and increased the drug releasing rate from floating tablets.

4- Partial replacement of sodium bicarbonate with calcium carbonate increased of both FLT and TFT and decreased in drug releasing rate from floating dosage form; Replacing Mcc by other types of diluents such as SDL and mannitol accelerated drug release and decreased in FLT and TFT.

5- F9 was the best formula (contain carbopol 934P as a hydrophilic polymer and mannitol as a diluent).

6- The estimated expiration data t using Arrhenius Plot for formula 9 was found to be (2.70) years.

7- For future work, one can make clinical study to determine the pharmacokinetics parameters in order to confirm the results of *in vitro* studies.

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