International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 14, Issue 6, 2022

Original Article

ENHANCEMENT OF LORATADINE DISSOLUTION BY SURFACE SOLID DISPERSION: THE POTENTIAL USE OF CO-PROCESSED EXCIPIENTS AS ON-SURFACE CARRIERS

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Received: 03 Aug 2022, Revised and Accepted: 08 Oct 2022

ABSTRACT

Objective: The aim of the work in this study is to enhance the dissolution rate of the poorly water-soluble drug; loratadine employing co-precipitated surface solid dispersions (SSDs) prepared using various hydrophilic on-surface carriers namely; Pearlitol® flash, Parteck® ODT, Prosolv® ODT G2 and Pharmaburst® C1.

Methods: Loratadine solid dispersions (SDs) were prepared by co-precipitation method using copovidone, poloxamer 188 and gluconolactone at different ratios. The best formulae were selected, based on dissolution results obtained, to prepare 16 different SSDs. The prepared SSDs were subjected to drug content and *in-vitro* dissolution studies and the best formulae were further subjected to solid-state characterization, using X-ray powder diffraction (XRPD) and differential scanning calorimeter (DSC). The effect of aging on the best formulae was studied by evaluating the drug content, drug dissolution and the change in the crystalline state using (XRPD).

Results: S1 formula, containing drug: poloxamer 188: pearlitol flash at 1:4:1 ratio, and S9 formula, containing drug: poloxamer 188: prosolv ODT at 1:4:1 ratio showed the highest dissolution efficiency. XRPD and DSC studies of S1 and S9 proved a decrease in drug crystallinity and confirmed solid dispersion formation. The stability study of S1 and S9 showed a slight reduction in the dissolution efficiency (DE) of S1 (from 84.6±0.8 to 81.4±0.7 and 81.4±1.3 at ambient and accelerated conditions, respectively) and a higher reduction in DE of S9 (from 83.5±2.4 to 69.6±1.0 and 57.3±2.9 at ambient and accelerated conditions respectively).

Conclusion: Results obtained obviously confirmed the potential effect of the surface solid dispersion technique, using poloxamer 188 as a hydrophilic carrier and Pearlitol flash as an on-surface carrier, on improving the dissolution of loratadine.

Keywords: Loratadine, Solid dispersion, Surface solid dispersion, Hydrophilic carriers, On-surface carriers, Dissolution improvement, Co-processed excipient

DOI: https://dx.doi.org/10.22159/ijap.2022v14i6.46059. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Oral administration of poorly water-soluble drugs, even those that have good dissolution in an acidic environment, often shows low and variable bioavailability due to incomplete and variable dissolution at the sites of absorption along the gastrointestinal tract (GIT) [1]. Therefore, it is important for such kinds of drugs to improve their solubility and enhance their dissolution rate.

The solid dispersion technique was among numerous techniques addressed to solve the problems related to poorly water-soluble drugs, its ability to enhance the dissolution characteristics of drugs with poor water solubility has been proved [2]. Despite the advantages of solid dispersion technology, it does have some disadvantages associated with it such as scale-up problems, physicochemical instability in the manufacturing process or during storage leading to phase separation and crystallization [3], tackiness and difficulty in handling the product [4].

Some of the problems associated with the properties of the SD technique can be easily overcome by using the SSD technique, which is a technique by which solid dispersion is formed and precipitated over the surface of an inert carrier. This strategy is used to reduce the agglomeration of the drug by increasing its exposed surface area in a way that would improve its dissolution rate [5]. The release of the drug from these carriers depends on the porosity, particle size and surface area of the carrier. When in contact with water, the carrier immediately disperses, allowing the rapid release of the drug [6]. SSD technique has been used to increase the solubility, dissolution and consequently the bioavailability of many practically insoluble or poorly water-soluble drugs such as Olmesartan [4], Irbesartan [7], Glibenclamide [8], Simvastatin [5], Carvedilol [9], Gliclazide [10] and Nifedipine [11].

Unlike the usual SD, carriers used in SSD are characterized by being water-insoluble, porous materials and hydrophilic in nature [12]. Examples of these carriers are sodium starch glycolate, croscarmellose, polyplasdone, silicon dioxide and microcrystalline cellulose [13], silicified microcrystalline cellulose, partially pregelatinized starch and starlac [4].

Loratadine is a second generation non-sedating tricyclic H1 antihistamine drug that prevents and suppresses seasonal and perennial allergic rhinitis, allergic dermatitis, urticaria and ocular allergy [14]. It is a white or almost white, crystalline powder with empirical formula; $C_{22}H_{23}ClN_2O_2$, a molecular weight of 382.9, a melting point of 134-136 °C and a dissociation constant of pKa 5. It is insoluble in water but very soluble in acetone, methanol, toluene and chloroform. The solubility of Loratadine in different pH media varied significantly with gastrointestinal tract pH range from 1.2 to 7.5 [1, 15, 16].

In this study, the SSD technique, using Pearlitol® flash, Parteck® ODT, Prosolv® ODT G2 and Pharmaburst® C1 as on-surface carriers, was applied to improve the dissolution of loratadine. To the best of our knowledge, no one used the same co-processed excipients as on-surface carriers to improve the dissolution of loratadine or any other drug.

MATERIALS AND METHODS

Materials

Loratadine was a gift from Sedico Pharmaceutical Co. (6th of October city, Egypt). Kolliphor®P188 (poloxamer 188), BASF, (Ludwigshafen, Germany). Plasdone® S630 (copovidone), was provided by Ashland (Schaffhausen, Switzerland). Gluconolactone was obtained from Jungbunzlauer, (Marckolsheim, France). Pearlitol® flash was supplied by Roquette (Lestrem, France). Parteck®ODT was obtained

from Merck, (Darmstadt, Germany). Prosolv® ODT G2 was supplied by JRS Pharma, (Rosenberg, Germany). Pharmaburst® C1 was provided by SPI Pharma, (Grand Haven MI, USA). Aerosil® 200 (colloidal silicon dioxide), was obtained from Evonik, (Hanau-Wolfgang, Germany). Ethanol 96%, El-Nasr Pharmaceutical Chemicals Co., (Cairo, Egypt). All other chemicals were reagent equivalent.

Methods

Preparation of SDs

Loratadine SDs were prepared by co-precipitation method using each of the hydrophilic carriers; Poloxamer 188, Copovidone and Gluconolactone in different drug: carrier weight ratios of 1:1, 1:2 and 1:4

Half gram of the drug and an accurately weighed suitable amount of each of the employed hydrophilic carriers were dissolved in the least amount of ethanol (in the case of Poloxamer 188 and Copovidone) or ethanol/water mixture 2/1 (in the case of Gluconolactone). The solvents were left to evaporate at room temperature [17]. The obtained solid masses were dried at 40 °C until constant weight, then passed through a 250 µm sieve and kept in a desiccator over anhydrous calcium chloride for further studies. Table 1 shows the compositions of the prepared SDs.

Table 1: Composition of loratadine SDs prepared by co-precipitation method

Formula	Hydrophilic carrier	Drug: Hydrophilic carrier ratio
D1	Copovidone	1:1
D2		1:2
D3		1:4
D4	Poloxamer 188	1:1
D5		1:2
D6		1:4
D7	Gluconolactone	1:1
D8		1:2
D9		1:4

Preparation of SSDs

Based on solid dispersions dissolution results obtained, the superiority of poloxamer 188 and gluconolactone as hydrophilic carriers in enhancing the dissolution rate of loratadine at a weight ratio of 1:4 was clearly seen. So they were selected as the carriers of choice to complete the study through the preparation of SSDs with different hydrophilic on-surface carriers, namely, Pearlitol® flash, Parteck® ODT, Prosolv® ODT G2 and Pharmaburst® C1.

SSDs of loratadine were prepared at a drug: hydrophilic carrier: hydrophilic on-surface carrier weight ratio of 1:4:1, 1:4:2 and 1:4:4. The preparation process was carried out by the co-precipitation method. The idea was to deposit the drug together with poloxamer 188 or gluconolactone as a solid solution onto the hydrophilic on-surface carrier.

Half gram of the drug and 2 g of poloxamer 188 or gluconolactone were dissolved in 10 ml ethanol or 10 ml ethanol/water mixture 2/1 respectively. Then, an accurately weighed suitable quantity of each of the employed hydrophilic on-surface carriers was suspended in this solution. The suspension was continuously stirred using a magnetic stirrer at room temperature till all the solvent evaporated. The obtained solid masses were dried at 40 °C until constant weight then passed through a 250 µm sieve and kept in a desiccator over anhydrous calcium chloride for further studies. It was observed that surface solid dispersions prepared with gluconolactone at the different weight ratios yielded tacky masses that were difficult to be processed. Adding Aerosil 200 and increasing the ratio of hydrophilic on-surface carrier to 1:4:6:2 (drug: gluconolactone: hydrophilic on-surface carrier: Aerosil 200) tackiness-free powder was obtained. Aerosil 200 was suspended with the hydrophilic on-surface carrier in drug/gluconolactone solution, then proceed as mentioned above. Table 2 shows the compositions of the prepared SSDs.

Determination of the drug content in the preparations

The solvent mixture was prepared by mixing water and ethanol at a ratio of 40:60 v/v, respectively. Accurately weighed samples equivalent to 5 mg of the drug were placed in a 50 ml volumetric flask, dissolved into 20 ml of the solvent mixture then the volume was made to 50 ml with the solvent mixture. This solution was filtered using GF/C microfiber filters. A 2 ml aliquot of the above-prepared solution was taken and diluted to 25 ml with the solvent mixture. The absorbance of the solution was determined by UV/VIS spectrophotometer (Nicolet evolution 100, Thermo Electron Corporation, England, UK) at the predetermined λ_{max} (248 nm) against the solvent mixture. All experiments were run in triplicate then the acceptance value (AV) was calculated using the following equation:

$$AV = |M - \bar{X}| + ks$$

Where M is a reference value; $\bar{X}$ is the mean value; k is the acceptability constant (equal to 2.4) and s is the sample standard deviation [18].

Table 2: Composition of loratadine SSDs prepared by co-precipitation method

Formula	Hydrophilic carrier		Hydrophilic on-surface carrier				
	Poloxamer 188	Gluconolactone	Pearlitol flash	Parteck ODT	Prosolv ODT	Pharmaburst	Aerosil 200
S1	4	-	1	-	-	-	-
S2	4	-	2	-	-	-	-
S3	4	-	4	-	-	-	-
S4	-	4	6	-	-	-	2
S5	4	-	-	1	-	-	-
S6	4	-	-	2	-	-	-
S7	4	-	-	4	-	-	-
S8	-	4	-	6	-	-	2
S9	4	-	-	-	1	-	-
S10	4	-	-	-	2	-	-
S11	4	-	-	-	4	-	-
S12	-	4	-	-	6	-	2
S13	4	-	-	-	-	1	-
S14	4	-	-	-	-	2	-
S15	4	-	-	-	-	4	-
S16	-	4	-	-	-	6	2

All S formulae contain 1 part of the drug.

***In-vitro* dissolution studies**

The USP standard dissolution apparatus II (AT 7 smart, Sotax AG, Switzerland). was used for studying the *in-vitro* dissolution of loratadine, prepared SDs and SSDs. An accurately weighed amount of each of the prepared systems equivalent to 5 mg loratadine, was placed in the dissolution vessels, containing 500 ml of phosphate buffer pH 6.8/0.05% *w/v* sodium lauryl sulfate solution. The paddle was rotated at 50 rpm and the temperature of the dissolution medium was maintained at 37 °C±0.5 °C. Samples of 4 ml aliquot were withdrawn at regular time intervals of 5, 10, 15, 30, 45 and 60 min and replaced with an equal volume of dissolution medium. Then the withdrawn samples were filtered using 0.45 µm Millipore filters. The filtered solutions were analyzed spectrophotometrically at the predetermined λ_{max} (248 nm) against the dissolution media. The *in-vitro* dissolution experiments were repeated in triplicate.

For assessment and comparison, the dissolution profile was evaluated on the basis of the dissolution efficiency parameter (DE) which is a model-independent parameter [19].

$$DE = \frac{\int_0^t yxdt}{y_{100}x\ t} X\ 100$$

Where the integration is the area under the dissolution curve up to dissolution time t, y is the percentage of drug dissolved at any time t and y100 is the area of the rectangle described by 100 % dissolution at the same time. Dissolution efficiency was calculated using DDSolver software program [20].

Solid state characterization

Fourier transform infrared spectroscopy (FT-IR) study was performed to investigate the compatibility of the drug with the used carriers. The solid state of the selected formulae was characterized using X-ray powder diffraction (XRPD) and differential scanning calorimeter (DSC) in comparison to the plain drug, carriers and physical mixtures.

Fourier transform infrared spectroscopy (FT-IR)

Samples of 2-3 mg were mixed with dry potassium bromide powder then compressed into discs under a pressure of 10 tons. The spectra of the plain drug, carriers, physical mixtures and the selected SSDs were scanned over a frequency range of 4000-400 cm^{-1}.

X-ray powder diffraction (XRPD)

Samples of the plain drug, the selected SSDs and the corresponding carriers and physical mixtures were evaluated with an X-ray powder diffractometer for the characterization of the crystalline phases. The samples were exposed to Cu Kα radiation generated at 1.5406 A° wavelength and scanned over a 2θ range from 10.0° to 70.0°. The output was given as intensity (recorded in count per second) versus 2θ. To compare the degree of crystallinity among formulae, the relative degree of crystallinity (RDC) was calculated according to the following equation:

$$RDC = I_{sam}/I_{drug}$$

where I_{sam} is the peak height of the sample under investigation and I_{drug} is the peak height of the drug with the highest intensity at the same angle [21].

Differential scanning calorimetry (DSC)

DSC analysis was performed using a model DSC-50 instrument calibrated with indium. Samples (2 mg) were placed in flat-bottomed aluminum sealed pan and heated at a constant rate of 25 °C/min, over a temperature range of 30-300 °C. The DSC studies were performed for the plain drug, the selected SSDs and the corresponding carriers and physical mixtures.

Effect of aging

Samples from the selected SSDs were filled in glass vials with rubber closures and aluminum seal then stored in a climatic chamber at 40 °C/75% relative humidity (RH) for 3 mo. The effect of aging was studied by evaluating the drug content, drug dissolution and the change in the crystalline state (using XRPD) then comparing the results with those stored under ambient conditions and the freshly prepared ones. Furthermore, the dissolution profiles of the stored samples were compared with the reference (dissolution data of the freshly prepared one) using the percentage of drug dissolved after 5 min (Q5), dissolution efficiency (DE60) and similarity factor (f2) which is defined by the following equation:

$$f2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} X\ 100 \right\}$$

Where n is the number of dissolution sampling times, R_t and T_t are the percent dissolved at each time point for the reference and test samples, respectively. An f2 value higher than 50 indicates that the two dissolution profiles are similar [22, 23].

Statistical analysis

All data were expressed as mean±SD. The obtained results were statistically analyzed using one-way analysis of variance (ANOVA) followed by Duncan test or least significant difference test (LSD) at ($P<0.05$) with the aid of Statistical Package for Social Sciences (SPSS) version 17.

RESULTS AND DISCUSSION

Drug content

Table 3 shows the average drug content of the prepared SDs and SSDs formulae. The drug content for all preparations ranged from 97.48±0.37% to 102.19±0.49%. Acceptance value (AV) was calculated to determine how far the drug content of the tested preparations varied with respect to the observed average. It was observed that both S6 and S9 showed the lowest AV (0.44), while the highest AV recorded was that of D7. However, all values were found to be within the limit (AV<15) which could be considered satisfactory to indicate a homogenous distribution of the drug in the prepared formulae [18].

***In-vitro* dissolution studies**

Dissolution of loratadine from SDs and SSDs in phosphate buffer pH 6.8/0.05% *w/v* sodium lauryl sulfate solution was performed, the cumulative percentage dissolved and the dissolution efficiencies at 5 min (DE5), 30 min (DE30) and 60 min (DE60) were calculated and compared to that of loratadine powder, table 3. Plain loratadine showed a poor dissolution extent, where the percentage of drug dissolved was 58.6% after 60 min with DE of 42.6. This result could be related to the weak base nature of loratadine which has a pKa value reported to be 5.52 and the dependence of loratadine solubility on pH, making it exhibits a good dissolution in acidic medium but dissolves poorly in alkaline medium [1].

Fig. 1 shows the dissolution of loratadine SD with copovidone at different ratios (1:1, 1:2 and 1:4). It was obvious that loratadine-copovidone SDs showed lower dissolution percent than the untreated drug. The obtained results were in contrast with the common trend of using copovidone to enhance the dissolution of poorly water-soluble drugs. For instance, Steve *et al.* found that the dissolution of Idasantulin was improved when incorporated in SD with copovidone where the drug was fully amorphous [24].

This decrease in drug dissolution could be attributed to the slow erosion of the SD arising from the reduced surface area due to the binding effect of copovidone [25, 26].

SDs of loratadine with poloxamer 188 at ratio 1:1 and loratadine showed nearly superimposed dissolution profiles. A marked increase in the percent of drug dissolved with increasing the ratio of drug to the carrier from (1:1) through (1:2) to (1:4) was observed as shown in fig. 2.

The previous observations could be attributed to the incomplete molecular dispersion of drug in the carrier at the lower ratio leading to the formation of drug aggregates which when comes into contact with the dissolution medium, poloxamer will form a viscous gel layer around the drug slowing down its dissolution, whereas in SDs

with a higher poloxamer ratio the drug could be dispersed molecularly among the carrier chain and therefore the formation of the glassy solution type of SD would be easy. When this system comes in contact with the dissolution medium, it will dissolve quickly relative to the wettability, emulsification and solubilisation effects of poloxamer 188 [27, 28].

Table 3: Drug content and dissolution efficiency of the different loratadine SDs and SSDs

Formula	Drug content %		Dissolution efficiency (DE)±SD		
	(Mean %±SD)	AV	5 min	30 min	60 min
loratadine	-	-	10.2±0.5	32.3±2.2	42.6±3.2
D1	100.37±1.34	3.21	1.6±0.3	3.6±0.7	5.1±1.3
D2	100.9±0.37	0.89	1.8±0.1	4.7±0.4	6.0±0.4
D3	100.58±0.37	0.89	2.3±0.3	5.0±0.3	5.7±0.4
D4	98.23±1.16	3.05	11.3±0.3	32.6±0.9	41.0±0.7
D5	100.05±1.65	3.95	15.1±0.2	39.8±1.0	48.6±0.5
D6	98.65±0.81	1.94	19.4±0.1	50.4±0.5	60.8±0.6
D7	98.65±1.77	4.24	3.1±0.1	14.6±0.3	20.7±0.7
D8	99.30±1.45	3.47	10.6±0.7	32.3±1.0	42.5±1.1
D9	100.05±1.13	2.71	15.1±0.8	47.1±1.9	60.6±1.4
S1	99.72±0.19	0.44	40.4±0.8	79.1±0.7	84.6±0.8
S2	98.44±0.19	0.5	36.9±0.7	71.9±1.2	77.3±1.3
S3	102.19±0.49	1.86	37.2±0.4	74.0±0.2	79.9±0.6
S4	99.83±0.32	0.77	10.7±0.4	35.0±0.5	47.1±0.7
S5	97.58±0.32	1.69	33.5±1.2	70.6±2.3	78.7±2.2
S6	99.72±0.19	0.44	36.4±0.3	74.1±0.5	80.6±0.8
S7	101.44±0.32	0.77	35.5±0.6	71.7±0.9	77.9±0.9
S8	101.65±0.67	1.75	19.7±0.8	53.1±1.1	65.3±1.5
S9	101.33±0.19	0.44	39.4±1.5	77.9±2.3	83.5±2.4
S10	98.01±0.49	1.66	32.2±0.9	69.1±1.5	76.2±1.8
S11	101.76±0.32	1.03	17.1±2.0	57.5±0.7	68.3±0.6
S12	97.48±0.37	1.91	11.9±0.6	36.8±0.5	49.6±0.6
S13	98.76±0.49	1.18	37.8±0.4	75.4±0.6	81.3±0.8
S14	102.08±0.32	1.35	37.1±0.2	75.2±0.8	81.2±1.2
S15	101.01±0.49	1.18	35.2±0.4	72.8±0.9	79.0±0.7
S16	99.51±0.64	1.54	13.2±0.3	43.4±2.4	56.8±2.7

Data expressed as mean±SD, n=3.

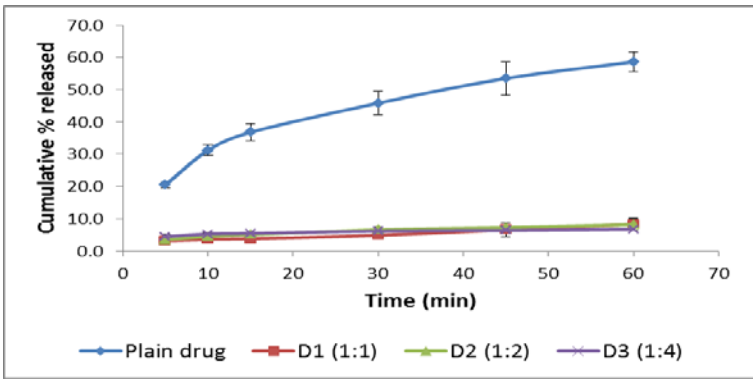

Fig. 1: Dissolution profiles of loratadine from the solid dispersions prepared with copovidone in phosphate buffer pH 6.8/0.05% w/v sodium lauryl sulfate solution. Data expressed as mean±SD, n=3

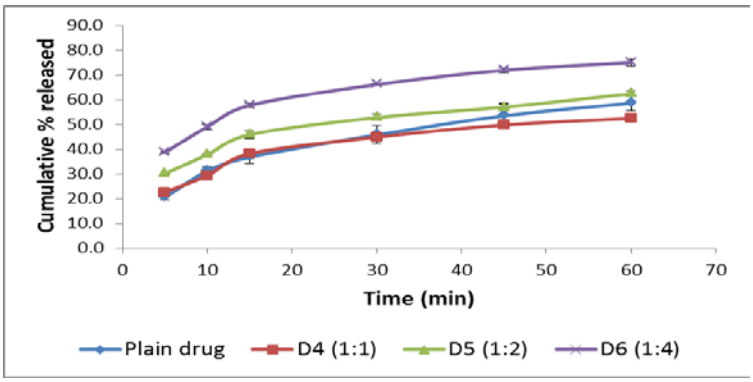

Fig. 2: Dissolution profiles of loratadine from the solid dispersions prepared with poloxamer in phosphate buffer pH 6.8/0.05% w/v sodium lauryl sulfate solution. Data expressed as mean±SD, n=3

Fig. 3 shows the dissolution data of loratadine from SDs with different gluconolactone ratios (1:1, 1:2 and 1:4). The data obtained showed that dispersion of loratadine into gluconolactone at 1:1 ratio resulted in a significant reduction in the cumulative percentage of drug dissolved while a non-remarkable improvement at 1:2 ratio was observed. Further increase in the amount of gluconolactone relative to the drug (1:4) ratio showed a remarkable enhancement in the cumulative percentage of drug dissolved.

The lower or the unchanged percent of the drug dissolved from SDs with the drug: carrier ratio of (1:1) and (1:2), compared to the plain drug, could be attributed to the formation of small crystals of the drug within the dispersion rather than remaining molecularly dispersed and/or due to insufficient amount of gluconolactone to mask the exposed hydrophobic surface of loratadine. On the other hand, the high percent of loratadine dissolved from solid dispersion with the drug: carrier ratio of (1:4) can be explained on the basis of the reduction of drug crystallite size (as proved later with DSC and XRD), a solubilisation effect of the carrier, absence of aggregation of drug crystallites, improved wettability and dispersibility of the drug, dissolution of the drug in the hydrophilic carrier, conversion of the drug to the amorphous state and finally the combination of the above-mentioned mechanisms [17]. Another explanation could be based on the acidic nature of gluconolactone, and since the solubility of loratadine is pH dependent; it shows high solubility at low pH media and poor solubility at high pH media, so high gluconolactone concentration will provide low pH microenvironment surrounding loratadine particles leading to increasing its dissolution in the medium of pH 6.8 [29].

Based on the above-mentioned dissolution results, Both D6 and D9 were selected for further studies where SSDs were prepared.

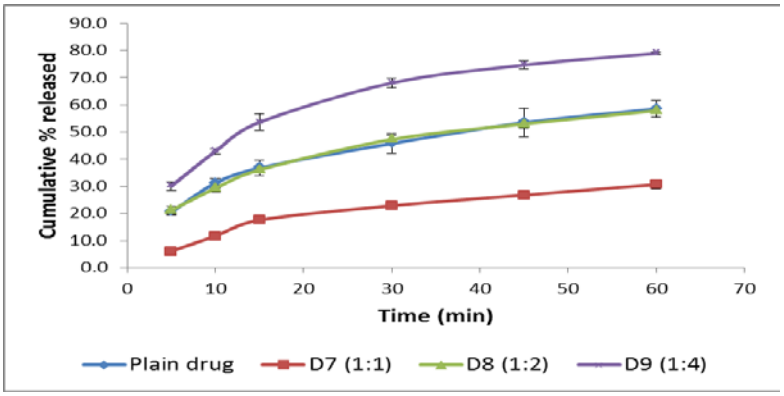

Fig. 3: Dissolution profiles of loratadine from the solid dispersions prepared with gluconolactone in phosphate buffer pH 6.8/0.05% w/v sodium lauryl sulfate solution. Data expressed as mean±SD, n=3

Dissolution of loratadine from the prepared SSDs in phosphate buffer pH 6.8/0.05% *w/v* sodium lauryl sulfate solution was performed and compared to their corresponding solid dispersions and the plain drug.

Fig. 4 shows the dissolution of loratadine SSDs with Pearlitol flash. It was obvious that the addition of Pearlitol flash as a hydrophilic on-surface carrier to D6 increased the percent of drug dissolved compared to the plain drug and D6. Rapid dissolution of the drug from the prepared SSDs was also observed, where the DE of loratadine after 5 min increased from 10.2 and 19.4 for the plain drug and D6, respectively to 40.4, 36.9 and 37.2 for S1, S2 and S3, respectively. This increase in drug dissolution can be attributed to the co-precipitation of drug and poloxamer as a solid solution at Pearlitol flash particles surface, creating a large surface area of drug exposed to the dissolution media. This combined effect of increased surface area and solid solution formation, augmented by good wettability provided by the association of starch and mannitol in Pearlitol flash composition [30], would explain the increase in drug dissolution from the prepared SSDs. Similar results were found by Essa *et al.* who found that the dissolution of Carvedilol from SSD with Avicel pH 101 as a carrier and Poloxamer 188 as a wetting agent was better than dissolution from SD with Poloxamer 188 alone, referring that to the dual effect of increased surface area augmented by solid solution formation in SSD technique [9].

The obtained data revealed that SSDs of loratadine with poloxamer as a hydrophilic carrier and Pearlitol flash as a hydrophilic on-surface carrier showed a significant reduction in DEs when the ratio of on-surface carrier increased from 1:4:1 (drug: poloxamer: Pearlitol flash) to 1:4:2. A further increase in Pearlitol flash ratio to 1:4:4 resulted in a non-significant increase in DEs compared to the 1:4:2 ratio. This might be due to the firm adsorption of the drug on Pearlitol flash at higher Pearlitol flash ratios, which hinders the dissolution of the drug. Similar results were obtained by Maulvi *et al.*, who found that the dissolution rate of Aceclofenac decreased at a higher drug: sylysia 350 ratios [31].

On the other hand, the addition of Pearlitol flash and Aerosil 200 as hydrophilic on-surface carriers to D9 resulted in a significant slight increase in the percent of drug dissolved compared to the plain drug and significant retardation of drug dissolution compared to D9. These results can be explained on the basis of using an ethanol/water mixture (2/1) to dissolve loratadine and gluconolactone, then when Pearlitol flash was added to this solution, the water-soluble part in Pearlitol flash; mannitol may have interrupted the solubility of gluconolactone in the available part of the preparation water, so gluconolactone left out the formed solid solution and upon solvent evaporation, loratadine precipitated alone as fine particles over Pearlitol flash particles creating a large surface area of the drug exposed to the dissolution media leading to an increase in the drug dissolution compared to the plain drug and a decrease in the drug dissolution compared to D9. Also, the combination of the drug and carrier at the molecular level in SDs leads to better wetting of the drug and hence better dissolution properties than SSDs [32].

Dissolution of loratadine from the SSDs prepared with Parteck ODT is shown in fig. 5. Data obtained showed that the adsorption of D6 on Parteck ODT enhanced drug dissolution compared to the plain drug and D6. This improvement in drug dissolution may be attributed to the co-precipitation of the drug and poloxamer as a solid solution at Parteck ODT particles surface, creating a large surface area of the drug exposed to the dissolution media. This combined effect of increased surface area and solid solution formation augmented by the good wettability and hydration provided by the combination of both water-soluble carrier; mannitol [5] and hydrophilic carrier; croscarmellose sodium [11] in the form of Parteck ODT would explain the increase in drug dissolution from the prepared SSDs.

Additionally, increasing the ratio of Parteck ODT from 1:4:1 to 1:4:2 to 1:4:4 (drug: poloxamer: Parteck ODT) resulted in a non-significant difference in DE60. These results are in agreement with that found by Tansel *et al.*, who found no significant change in the wetting time values and water absorption ratios of Rasagiline OD tablets when the level of Parteck ODT increased from 3.8% to 7.6%.

They referred this to the high content of spray-granulated mannitol in Parteck ODT composition making mannitol`s effect on wetting time and water absorption superior to croscarmellose sodium [33].

Similar results of dissolution improvement were also obtained when Parteck ODT and Aerosil 200 were added as hydrophilic on-surface carriers to D9.

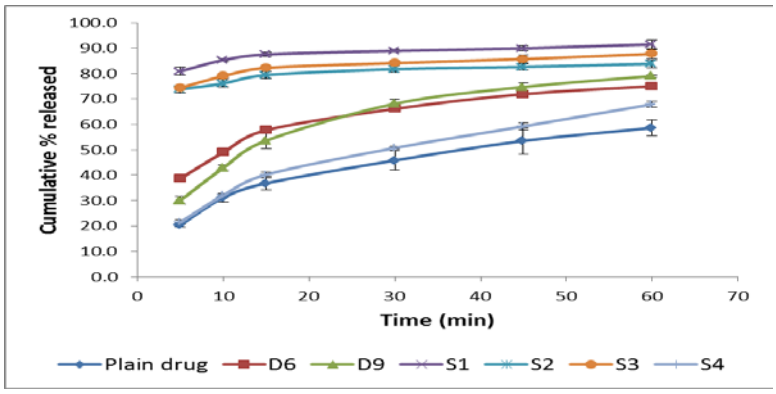

Fig. 4: Dissolution profiles of loratadine from the surface solid dispersions prepared with Pearlitol flash, data expressed as mean±SD, n=3

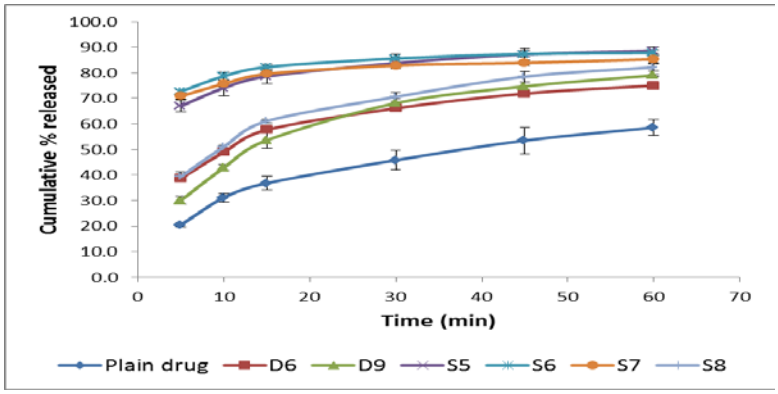

Fig. 5: Dissolution profiles of loratadine from the surface solid dispersions prepared with Parteck ODT. Data expressed as mean±SD, n=3

Fig. 6 shows the dissolution of loratadine from the SSDs prepared with Prosolv ODT. It was obvious that the adsorption of D6 on Prosolv ODT resulted in enhanced drug dissolution compared to the plain drug and D6. This improvement in drug dissolution may be explained on the basis of the combined effect produced by solid solution formation and precipitation at Prosolv ODT particles, which have good wettability and hydration provided by the combination of both water-soluble carriers; mannitol [5] and fructose and hydrophilic carriers; crospovidone [34], microcrystalline cellulose and colloidal silicon dioxide [4] in its composition.

Moreover, the increase in Prosolv ODT content in SSD from 1:4:1 to 1:4:2 to 1:4:4 (drug: poloxamer: Prosolv ODT) resulted in a significant decrease in DEs. This was attributed to the complex structure of Prosolv ODT as it contained three adsorbent materials in its composition; microcrystalline cellulose, colloidal silicon dioxide and crospovidone, so increasing the ratio of Prosolv ODT might lead to firm adsorption of the drug on Prosolv ODT particles and hence reduced drug dissolution [35, 36].

On the other hand, adsorption of D9 on Prosolv ODT and Aerosil 200 resulted in a slight increase in the DE after 5 min compared to the plain drug, where S12 showed 11.9 against 10.2 for the plain drug. After 30 min a DE of 36.8 was observed for S12 relative to 32.3 for the plain drug, while after 60 min the DE increased from 42.6 for the plain drug to 49.6 for S12. The enhancement in the DE was lower for S12 compared to its corresponding SD; D9. Explanation similar to that is used with Pearlitol flash can be applied with Prosolv ODT also.

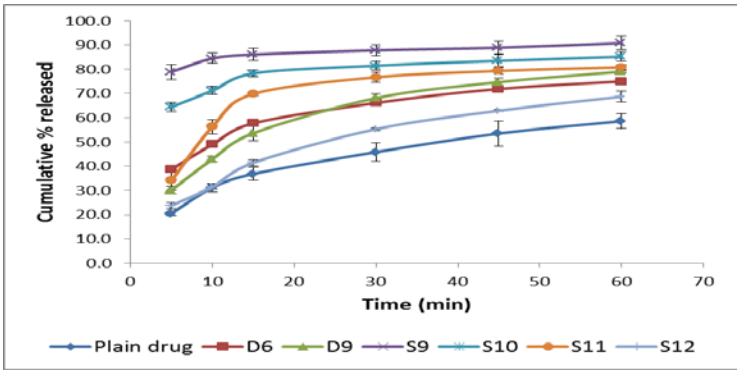

Fig. 6: Dissolution profiles of loratadine from the surface solid dispersions prepared with Prosolv ODT. Data expressed as mean+SD, n=3

The effect of using Pharmaburst as a hydrophilic on-surface carrier on the dissolution of loratadine is shown in fig. 7. Data obtained showed enhanced dissolution when D6 was adsorbed on Pharmaburst, compared to the plain drug and D6. This improved dissolution can be attributed to the dual effect produced by solid solution formation with poloxamer, which has a good solubilizing and wetting effect, and co-precipitation at Pharmaburst particles, which has a large surface area, good wettability and good hydration provided by the combination of both water-soluble carriers; mannitol [8] and sorbitol and hydrophilic carriers; crospovidone [34], and silicon dioxide [4] in its composition.

A non-significant reduction in DE60 with increasing the amount of Pharmaburst was observed. This might be due to the high content of mannitol in Pharmaburst composition; thus, the increased amount of Pharmaburst had a no-significant effect on DE due to the very minimal water uptake of mannitol [37].

On the other hand, adsorption of D9 on Pharmaburst and Aerosil 200 was found to increase the DE compared to the plain drug. The increase in the DEs of S16 was lower compared to that of D9. Explanation similar to that is used with Pearlitol flash can be extrapolated to Pharmaburst also.

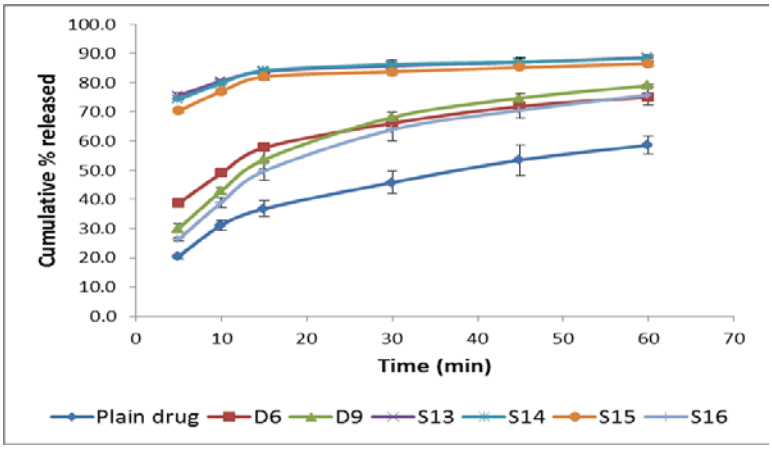

Fig. 7: Dissolution profiles of loratadine from the surface solid dispersions prepared with Pharmaburst. Data expressed as mean+SD, n=3

It was possible to point out from table 3 that the highest DEs were recorded for S1 as well as S9; both were non-significantly different (p=0.406). Therefore, both S1 and S9 were subjected to further investigations.

Solid state characterization of selected loratadine SSDs

Infrared studies

The IR study was conducted to examine if an interaction between loratadine and the tested carriers and on-surface carriers could occur. The IR studies were carried out for the plain drug, the selected, tested carrier (poloxamer 188), on-surface carriers (Pearlitol flash and Prosolv ODT) and drug-carrier or on-surface carrier (1:1) physical mixtures. The spectra were shown in fig. 8.

The spectral analysis of plain drug showed many characteristic bands, band at wave number 1700 cm^{-1} due to the C=O stretching, bands at 1437 cm^{-1}, 1225 cm^{-1} and 1105 cm^{-1}due to C-O stretching, and bands from 3000 cm^{-1} to 2880 cm^{-1} corresponds to C-H stretching [38-40].

Further, the IR spectra of the prepared physical mixtures of the drug with the selected, tested carrier and on-surface carriers are largely similar to the addition spectra of similar components. The IR spectra didn't show any new functional groups formed, conforming that no chemical interaction between the drug and the used carrier or on-surface carriers. The decrease in the intensity of the band absorbance can be attributed to the decrease in the amount of the components in the prepared Physical mixture.

Fig. 9 shows the IR spectra of the selected surface solid dispersion formulae (i.e. S1 and S9). The obtained spectra displayed the characteristic peaks of their respective components at the same position appearing for each constituent when analyzed alone. The decrease in the intensity of C=O band of loratadine at 1704 cm^{-1} and the difficulty in detecting other characteristic bands of loratadine can be attributed to low drug content in the prepared SSDs or being masked by the carrier absorption band at the same position. There were no new bands observed in the spectrum; this suggested the absence of molecular interaction between the components of either formulation studied.

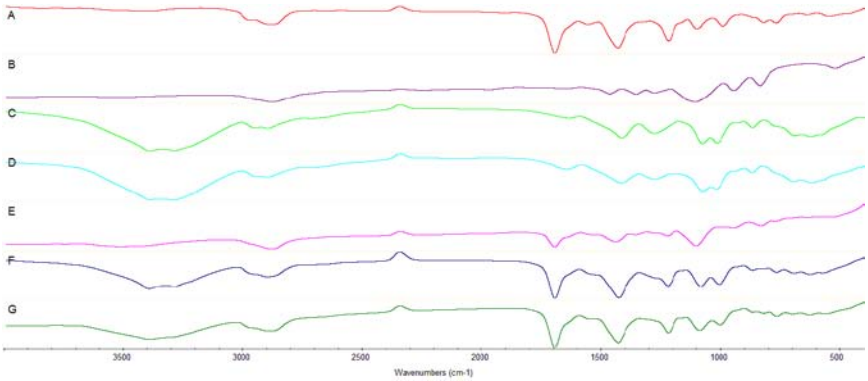

Fig. 8: IR Spectra of Loratadine (A), Poloxamer 188 (B), Pearlitol flash (C), Prosolv ODT (D), Loratadine+ Poloxamer 188 (E), Loratadine+Pearlitol flash (F), Loratadine+Prosolv ODT (G)

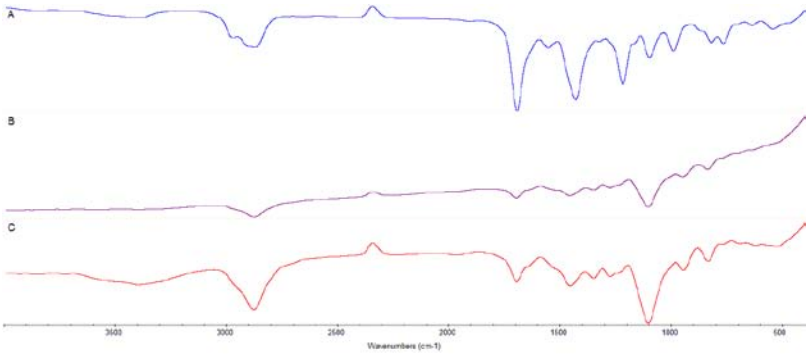

Fig. 9: IR Spectra of Loratadine (A), S1 (B) and S9 (C)

X-ray diffraction studies

The diffraction pattern of loratadine as shown in fig. 10A shows that the drug has high crystallinity because of the presence of numerous distinct peaks at 2θ diffraction angles. These peaks are located at 12.8, 15.1, 16.4, 19.5, 21.0, 23.7 and 24.3 degrees.

The diffraction pattern of poloxamer 188 showed 2 characteristic peaks while that of Pearlitol flash and Prosolv ODT showed numerous diffraction peaks indicating their crystalline nature as shown by fig. (10B, 10C and 10D).

From fig. (10E, 10F and 10G), the x-ray diffraction patterns of loratadine-poloxamer 188, loratadine-pearlitol flash and loratadine-Prosolv ODT (1:1) physical mixtures showed superposition of the spectra of each component with a slight reduction in the intensity of loratadine characteristic peaks due to dilution effect. This indicated that the drug was still in the crystalline state in the prepared physical mixtures [41].

On the other hand, from fig. 11, the x-ray diffraction patterns of the selected surface solid dispersion formulae; S1 and S9 showed a reduction in the intensity and number of typical diffraction peaks of loratadine, suggesting a reduction in the crystalline nature of the drug and may be a conversion of the drug from the crystalline state to the amorphous one [7].

A plain drug peak at 19.475° 2θ was used for calculating the RDC. The calculated RDC values were 0.349 and 0.360 for S1 and S9, respectively. These values suggested the reduction in loratadine crystallinity in S1 and S9 compared to the plain drug and that S1 showed a degree of crystallinity slightly smaller than that of S9.

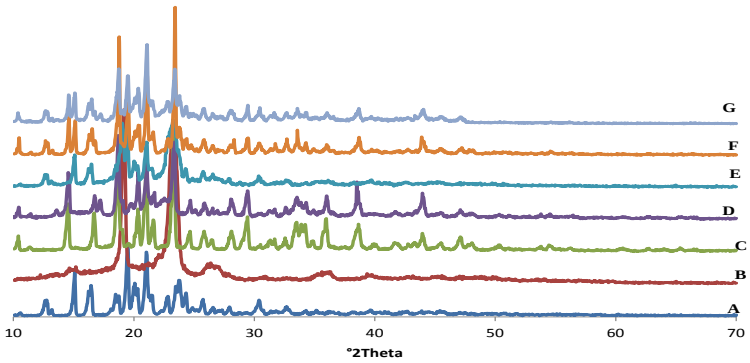

Fig. 10: X-ray diffraction of Loratadine (A), Poloxamer 188 (B) Pearlitol flash (C), Prosolv ODT (D), Loratadine+ Poloxamer 188 (E), Loratadine+Pearlitol flash (F) and Loratadine+Prosolv ODT (G)

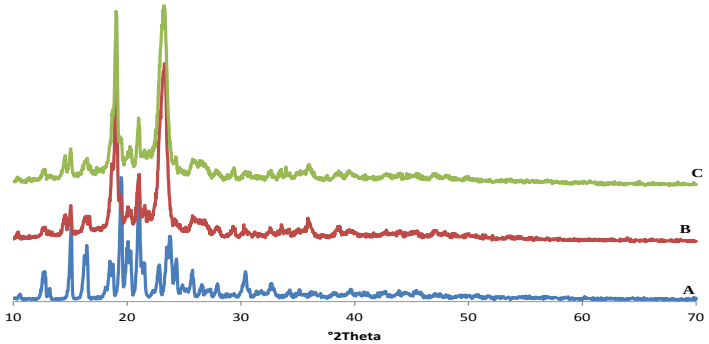

Fig. 11: X-ray diffraction of Loratadine (A), S1 (B) and S9 (C)

Differential scanning calorimetry (DSC)

As shown in fig. 12, the DSC thermogram of loratadine showed a sharp endothermic peak at 136.0 °C, corresponding to its melting point [42].

The DSC thermogram of poloxamer 188 showed a sharp peak at 53.0 °C [43], while Pearlitol flash and Prosolv ODT showed one characteristic endothermic peak at 165.0 °C and 158 °C, respectively due to the mannitol base of the co-processed excipients [44].

The DSC thermogram of the physical mixture of the drug and poloxamer 188 at a 1:1 ratio showed the characteristic peak for poloxamer 188 at 46.0 °C and a very low-intensity peak of the drug shifted to a lower melting point; 125.0 °C. This may be attributed to the dissolution of the drug in melted poloxamer 188 during measurement and so, only one characteristic endothermic peak corresponding to the melting of poloxamer 188 was observed. This finding is in agreement with the report of Yamashita *et al.*, which reported the absence of the endothermic peak of tacrolimus in the physical mixture of tacrolimus with PEG 6000 [45]. The DSC thermogram of the physical mixture of the drug and Pearlitol flash or Prosolv ODT at a 1:1 ratio showed characteristic peaks for both drug at about 132.0 °C, Pearlitol flash at 164.0 °C and Prosolv ODT at 160 °C with no additional peaks.

On the other hand, fig. 13 shows the DSC thermogram of S1 and S9 with only the peak of poloxamer 188 at about 50.0 °C and the peak of Pearlitol flash or Prosolv ODT at about 166.0 °C with the disappearance of the drug peak indicating a decrease in drug crystallinity and confirmed that a solid dispersion was obtained and the crystalline drug was converted to the amorphous form [4, 46].

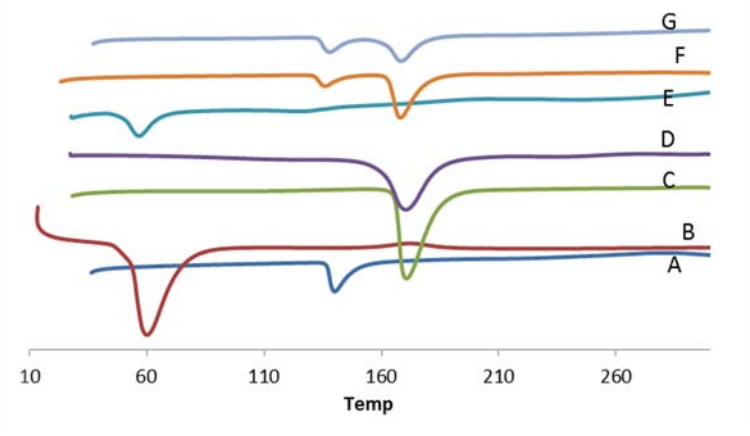

Fig. 12: DSC thermogram of Loratadine (A), Poloxamer 188 (B), Pearlitol flash (C), Prosolv ODT (D), Loratadine+Poloxamer 188 (E), Loratadine+Pearlitol flash (F) and Loratadine+Prosolv ODT (G)

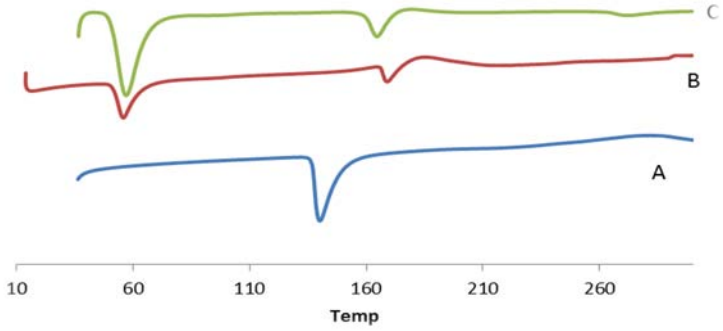

Fig. 13: DSC thermogram of Loratadine (A), S1 (B) and S9 (C)

Effect of aging

Accelerated stability studies were carried out as per ICH guidelines (40 °C/75% RH) for a period of up to three months to determine the effect of aging on the performance of the selected formulae; S1 and S9 [47]. The selected formulae were characterized by performing drug content determination, *in-vitro* drug dissolution and XRPD studies after the first, second and third month, then comparing the results with those stored under ambient conditions and freshly prepared ones.

Table 4 shows the average drug content of the selected formulae stored at ambient and accelerated conditions. All values were found to be within the limit (less than 5% change from the initial value), which could be considered satisfactory to indicate the chemical stability of S1 and S9 throughout the study period [47].

Table 4: Drug content of S1 and S9 stored at ambient and accelerated conditions

Time	Average drug content (%)*			
	S1		S9	
	Ambient	40 °C/75% RH	Ambient	40 °C/75% RH
Initial	99.72±0.19	99.72±0.19	101.33±0.19	101.33±0.19
1st month	98.98±0.49	97.91±1.47	100.58±0.74	98.55±0.64
2nd month	97.91±0.56	97.58±0.64	100.05±0.67	98.23±0.32
3rd month	98.65±0.98	97.69±0.81	99.40±0.49	98.12±0.19

*mean±standard deviation, n=3

In-vitro drug dissolution of the selected formulae; S1 and S9 was monitored at ambient and accelerated (40 °C/75% RH) conditions for three months.

For a better assessment of the effect of aging on the dissolution of the selected formulae, the dissolution profiles of the stored samples were compared with the reference (dissolution profiles of the freshly prepared ones) using the percentage of drug dissolved after 5 min (Q5) together with two model-independent parameters; dissolution efficiency (DE60) and similarity factor (f2).

As shown in fig. 14, rapid dissolution of the drug from S1 was retained during the three months stability study, where the average percent of loratadine dissolved after 5 min (Q5) was 83.3% (p = 0.079), 86.6% (p = 0.001) and 80.4% (p = 0.710) for the samples stored at ambient conditions after the first, second and third month, respectively, while samples stored at 40 °C/75% RH showed Q5 of 81.9% (p = 0.556), 79.6% (p = 0.447) and 79.4% (p = 0.404) after the first, second and third month respectively compared to initial Q5 of 80.9%.

Based on the statistical analysis conducted on S1 formula using one-way ANOVA ($p<0.05$) and Post Hoc LSD test, the DE60 differences between the initial sample and samples stored at ambient conditions for the first two months were reasonably insignificant, while samples stored for three months showed a slight reduction in DE60, (p= 0.698, 0.510 and 0.025 for the first, second and third month, respectively). Samples stored at 40 °C/75% RH for one month showed an insignificant difference in DE60, while samples stored for two and three months showed a significant reduction in DE60 (p = 0.074, 0.001 and 0.002 for the first, second and third months, respectively) compared to the initial sample.

The similarity factor (f2) for S1 formula stored at ambient and accelerated (40 °C/75% RH) conditions for three months was calculated using dissolution data of the fresh sample as a reference profile. Similarity factor for all periods studied for stability was higher than 50 (f2= 78.7, 72.2 or 71.7 for samples stored at ambient conditions after the first, second and third month, respectively while at 40 °C/75% RH, f2 was 80.4, 70.1 or 71.4 after the first, second and third month, respectively) indicating that the dissolution profile patterns of S1 formula after stability were similar to the initial one.

On the other hand, S9 formula showed a slower dissolution rate during the three months stability period than the initial sample, as shown in fig. 15. The amount of drug dissolved decreased with increasing storage time and with increasing temperature and humidity, where Q5 was 62.5% (p = 0.000), 61.0% (p = 0.000) and 56.0% (p = 0.000) for the samples stored at ambient conditions after the first, second and third month, respectively while samples stored at 40 °C/75% RH showed Q5 of 58.2% (p = 0.000), 46.5% (0.000) and 41.3% (p = 0.000) after the first, second and third month, respectively relative to initial Q5 of 78.9%.

Statistical analysis of DE60 of S9 formula stored at ambient and 40 °C/75% RH showed a significant reduction in DE60 (p=0.000) for all periods studied compared to the initial sample. This was confirmed by the calculation of the similarity factor between the dissolution profiles of fresh and aged samples. The values of the similarity factor were lower than 50 (f2=49.5, 44.0 and 39.5 for the samples stored at ambient conditions after the first, second and third month, respectively, while at 40 °C/75% RH, f2 was 41.4, 31.0 and 26.6 for the first, second and third month, respectively) indicating that the dissolution profile pattern of S9 formula changed upon storage and became dissimilar to the initial one. This reduction in drug dissolution from S9 formula can be attributed to the complex structure of prosolv ODT as it contained beside mannitol and fructose three adsorbent materials; microcrystalline cellulose, crospovidone and colloidal silicon dioxide, which increased moisture uptake by the sample stored under high humidity conditions, this led to phase separation of drug/poloxamer SD from Prosolv ODT and re-crystallization of the drug during the stability period as shown later by X-ray diffraction study [48].

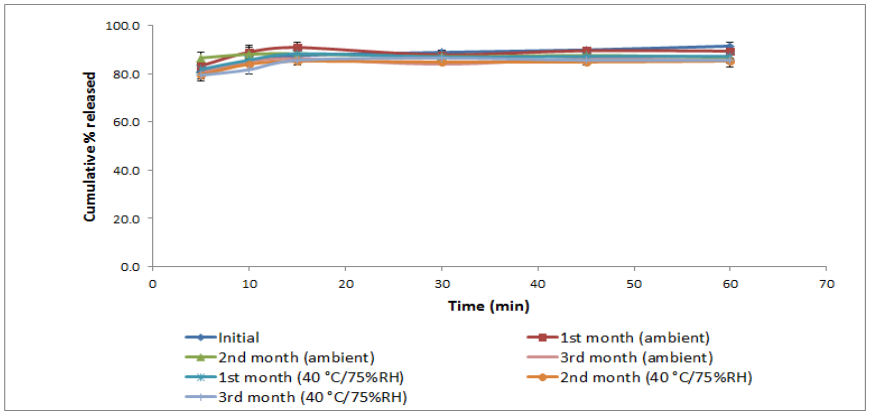

Fig. 14: *In-vitro* dissolution of loratadine from S1 throughout three months of storage at ambient conditions and 40 °C/75%RH. Data expressed as mean±SD, n=3

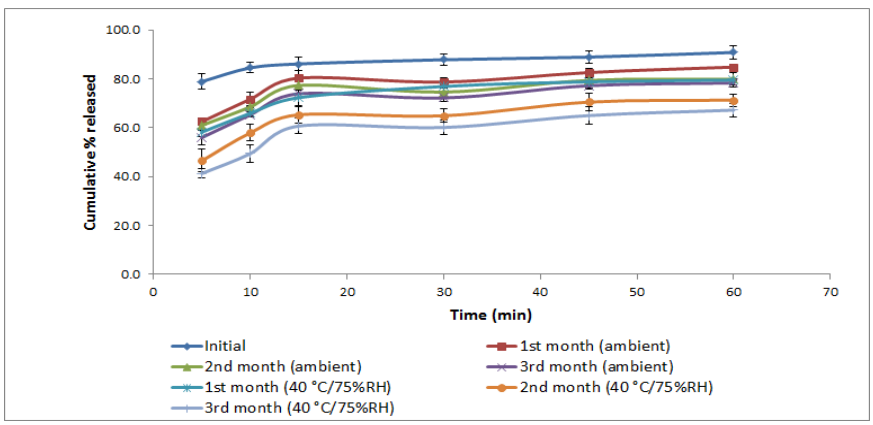

Fig. 15: *In-vitro* dissolution of loratadine from S9 throughout three months of storage at ambient conditions and 40 °C/75%RH. Data expressed as mean±SD, n=3

The X-ray diffraction patterns of the selected formulae; S1 and S9, directly after preparation and throughout 3 mo of storage at ambient and accelerated (40 °C/75% RH) conditions are shown in fig. (16 and 17). At ambient conditions, it was observed that both S1 and S9 showed similar X-ray diffraction patterns when compared to the freshly prepared samples suggesting the preservation of the partially amorphous state of loratadine in the dispersions.

On the other hand, the diffractogram of S1 and S9 samples stored at 40 °C/75% RH showed the reappearance of diffraction peaks, growing with time, at °2θ = 12.8 and 24.3 consistent with the crystalline loratadine diffraction peaks as shown in the spectra after the first, second and third month, suggesting the recrystallization of the drug in both formulae.

At 40 °C/75% RH, S9 showed a higher increase in the height of re-appearing diffraction peaks with time, suggesting faster recrystallization of the drug than that in S1; this can be attributed (as explained earlier in the drug dissolution stability study) to the presence of three adsorbent materials in the composition of prosolv ODT against one adsorbent material in the composition of Pearlitol flash, this led to higher moisture uptake followed by faster re-crystallization of the drug from S9 than from S1.

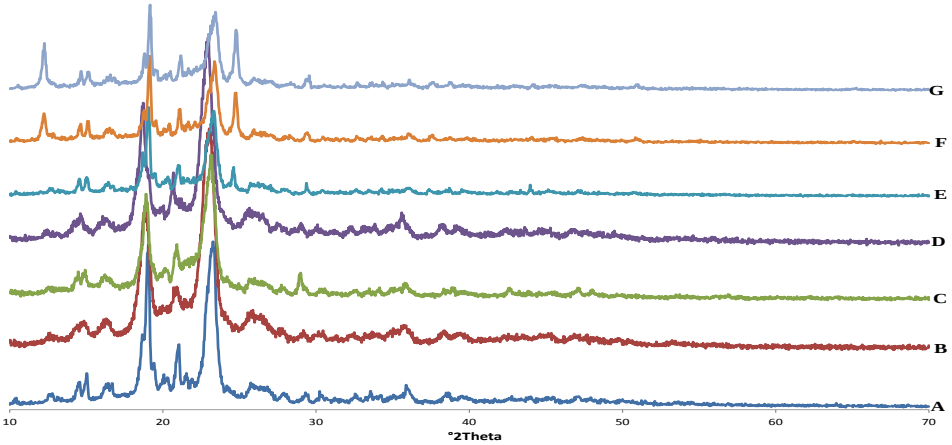

Fig. 16: X-ray diffraction of S1 throughout three months of storage at ambient and accelerated conditions (A) initial, (B) 1st mo (ambient), (C) 2nd mo (ambient), (D) 3rd mo (ambient), (E) 1st mo (accelerated), (F) 2nd mo (accelerated) and (G) 3rd mo (accelerated)

The re-crystallization of the drug from S1 and S9 samples stored at 40 °C/75% RH led to a decrease in drug dissolution and DE compared to the freshly prepared ones. The slight increase in the crystallinity of loratadine in S1 was insufficient to produce a significant change in the dissolution profiles of the stored samples, as confirmed by the values of f2 greater than 50, while faster drug recrystallization from S9 than from S1 led to superiority of S1 over S9 concerning the preservation of drug dissolution and DE.

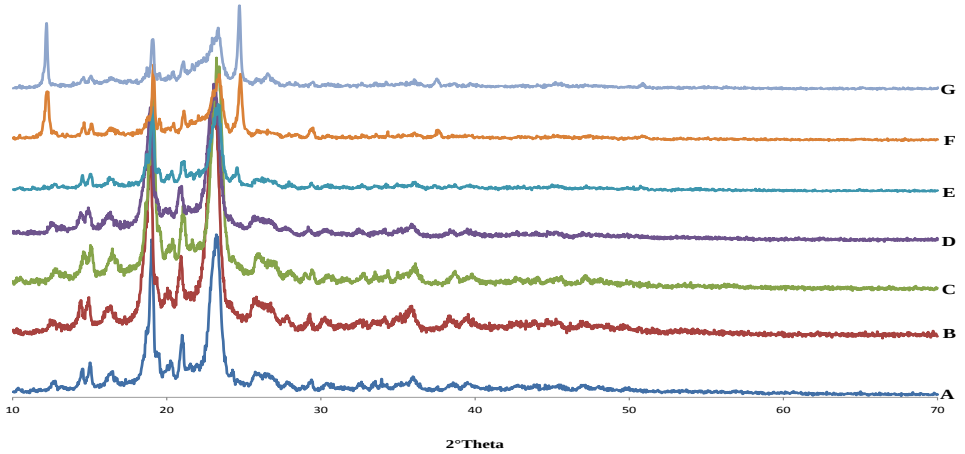

Fig. 17: X-ray diffraction of S9 throughout three months of storage at ambient and accelerated conditions (A) initial, (B) 1st mo (ambient), (C) 2nd mo (ambient), (D) 3rd mo (ambient), (E) 1st mo (accelerated), (F) 2nd mo (accelerated) and (G) 3rd mo (accelerated)

CONCLUSION

The dissolution of Loratadine was successfully improved using the surface solid dispersion technique employing poloxamer 188 and gluconolactone as hydrophilic carriers and Pearlitol flash, Parteck ODT, Prosolv ODT, and Pharmaburst as on-surface carriers. S1 (based on poloxamer 188 and pearlitol flash) and S9 (based on poloxamer 188 and Prosolv ODT) formulae showed the highest dissolution efficiency as a result of the reduction in drug crystallinity and solid dispersion formation, as proved by PXRD and DSC studies.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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