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Design and Evaluation of Effervescent Powder Formulations of a Novel Combination of Ketoprofen, Pseudoephedrine HCl and Levocetirizine dihydrochloride

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ABSTRACT

Many OTC products are available to relieve the symptoms associated with common cold. However, to the best of our knowledge, no drug product containing ketoprofen, pseudoephedrine HCl and levocetirizine dihydrochloride is available in the drug market. Therefore, this study aimed to design and evaluate appropriate effervescent powder formulations of a novel combination of the three drugs. Nine formulations containing 50 mg, 60 mg and 2.5 mg of the relevant drugs, respectively, were prepared. Each formulation contained mannitol, lactose or starch as diluent and a definite concentration of the effervescent base which was composed of citric acid, tartaric acid and sodium bicarbonate. The drug content, powder characterization, moisture content, effervescence time and pH of aqueous solution of each formulation were initially investigated. It was found that the mannitol-included (FM) and starch-included (FS) formulations demonstrated larger bulk density, better flowability and faster effervescence times than lactose-included formulations (FL) and hence, were selected to undergo in vitro drug release testing. Among the tested formulations, only (FS3) and (FM3), which contained 89.9% concentration of effervescent base, demonstrated approximately 100% drug release after 5 minutes. Eventually, upon testing the stability of those 2 formulations, (FS3) showed longer shelf-lives of the three drugs than those obtained with (FM3).

Keywords: Ketoprofen; Pseudoephedrine HCl; Levocetirizine dihydrochloride; Common cold; Effervescent powder

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INTRODUCTION

The common cold (also known as nasopharyngitis, acute viral rhinopharyngitis, acute coryza, or a cold) is a viral infectious disease of the upper respiratory system [1]. Signs and symptoms of the disease include cough, sore throat, runny nose, sneezing, headache, and fever [1,2].

There are no effective antiviral drugs for the disease even though some preliminary research has shown benefits [3]. Many OTC medications are available to treat cold and flu symptoms. The conventional therapy involves a combination of OTC drugs such as antihistamines, decongestants and antipyretics [1,4].

Ketoprofen (2-(3-benzoylphenyl)-propionic acid) is a potent non-steroidal anti-inflammatory drug (NSAID) used for the treatment of a wide range of painful and inflammatory illness [5]. The drug also has been widely used for the treatment of pain and fever associated with the common cold [6]. Pseudoephedrine HCL, [1S,2S]-2-methylamino-1-phenylpropan-1-ol] hydrochloride, is an alpha-adrenergic agonist used as a nasal decongestant in patients with allergic rhinitis and in acute rhinitis in patients with upper-respiratory infections. It is a stereoisomer of ephedrine and is less potent than ephedrine in producing tachycardia and CNS stimulation [7]. Levocetirizine dihydrochloride, (2-(4-R)-(4-Chlorophenyl)(phenyl)methyl] piperazin-1-yl) ethoxy) acetic acid dihydrochloride, is the (R) enantiomer of cetirizine. It is a third generation non-sedative H1-histamine receptor antagonist. [8,9].

Effervescent mixtures have been moderately popular over the years since along with the medicinal value of the particular preparation, they offered the public a unique dosage form that was interesting to prepare. These solid oral dosage forms can produce quicker and more complete drug absorption than tablets or capsules and provide a pleasant taste, due to carbonation, which helps to mask the objectionable taste of the drugs. The effervescent base is usually composed of sodium bicarbonate, citric acid and tartaric acid. When added to water, the acids and base react to liberate carbon dioxide, resulting in effervescence [10].

To the best of our knowledge, no OTC medication containing the three relevant drugs is available in the drug market.

EXPERIMENTAL SECTION

Materials

Ketoprofen (BASEF, Germany), Levocetirizine dihydrochloride, Pseudoephedrine HCl, paracetamol, (Springer, Germany), were a kind gift from Global pharma company (Sana' a, Yemen). Methanol, acetonitrile and triethylamine HPLC- grade (Springer, Germany) were purchased from the market. Other purchased materials were at least of analytical grade.

Instrumentations

HPLC equipment (LC2000 Jasco- Japan) supplied with a solvent delivery pump (PU 2089) and attached to UV detector(Jasco,2070) , ChromNAV software and C18 column (Analytical Capital limited,UK) (250 mm x 4.6 mm, 5 μm); Fourier- transform Infrared (FT-IR) spectroscopy (IRAffinity-1S , Shimadzu, Japan).

Compatibility Study

Fourier-transform infrared (FT-IR) spectra were obtained using an FT-IR spectroscopy. Firstly, reference standards of the drug were investigated alone. Then, a physical mixture of the drugs with excipients was investigated . The sample was ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press [10,11]. The range of IR scanning was between 2000- 500cm-1.

Preparation of Effervescent Powder Formulations

Nine formulations (Table 1) were prepared by geometric mixing. Each one of the prepared formulation contained 50 mg of ketoprofen, 60 mg of pseudoephedrine HCl and 2.5 mg of levocetirizine dihydrochloride. The diluent included in each formulation was mannitol, lactose or starch. Hence, they were coded as (FM, FL and FS), respectively. All formulations contained an effervescent base composed of citric acid, tartaric acid and sodium bicarbonate. The concentration of effervescent base was 80.5%, 85.1% or 89.9%, but the proportion among the three ingredients of the base, in each formulation, was maintained as (1: 2: 3.44), respectively, as described in the literature [12]. However, a concentration of 1.5% of sodium benzoate was included as a lubricant, in each formulation, to improve powder flow. Sufficient quantities of a sweetener, colorant and flavor were included in each formulation.

Table 1: Formulations of effervescent powders (4 g) prepared in this study

Ingredient	Formulation code								
	Amount as mg/formulation								
	FM1	FM2	FM3	FL1	FL2	FL3	FS1	FS2	FS3
Ketoprofen	50	50	50	50	50	50	50	50	50
Pseudoephedrine HCl	60	60	60	60	60	60	60	60	60
Levocetirizine dihydrochloride	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Citric acid	500	510	558	500	510	558	500	510	558
Tartaric acid	1000	1000	1120	1000	1000	1120	1000	1000	1120
Sodium bicarbonate	1720	1895	1860	1720	1895	1860	1720	1895	1860
Sodium benzoate	64	64	64	64	64	64	64	64	64
Lactose monohydrate	-	-	-	543.5	358.5	166.5	-	-	-
Starch	-	-	-	-	-	-	543.5	358.5	166.5
Mannitol	543.5	358.5	166.5	-	-	-	-	-	-
Sweetener, flavor,	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Color									
% of	80.5	85.1	89.9	80.5	85.1	89.9	80.5	85.1	89.9
Effervescent base									

Evaluation of the formulations

The evaluation of formulations was carried out in 3 consecutive stages.

Stage (1)

The stage involved analysis of drug content, physical characterization of powder, moisture content, effervescence time and pH of aqueous solution. The aim of that stage was to select the formulations having the best characters for further investigations.

Drug content

Two systems (I and II) of HPLC were used for analysis of the contents of the three drugs in the effervescent powder formulations. The systems utilized the same HPLC equipment but with different mobile phase and UV detection wavelengths. The system (I) involved isocratic elution of a mobile phase consisting of a mixture of methanol, acetonitrile and 1.5% sodium acetate solution (15:35:50 v/v/v) and UV detection at 240 nm. This was used for ketoprofen assay as described by Boyka et al. [13]. On the other hand, the system (II) was used for determination of pseudoephedrine HCl and Levocetirizine dihydrochloride as described by Gonjare et al. [14]. The system involved programmed gradient consequent elution of 2 mobile phases (A and B) and both phases consisted of a mixture of triethylamine solution (1 mL dissolved in 1000 mL of purified water, pH adjusted to 3 by orthophosphoric acid)) and acetonitrile but at ration of (85: 1 v/v) for phase (A) and (40:60 v/v) for phase (B). The phase (A) eluted first for

10 minutes, followed by the mobile phase (B) for 8 minutes and latterly the phase (A) eluted again for 7 minutes. The detection was carried out by UV absorbance at 210 nm. For both systems (I and II), the flow rate of mobile phase was 1 mL/min.

Prior to assay, the standard calibration curve of each drug in the analytical method was constructed by analysis standard reference solutions of the drugs. For that purpose, a stock standard solution (400 µg/mL) of ketoprofen was prepared by dissolving 20 mg of the drug up to 100 mL of the mobile phase. Serial dilutions using the mobile phase were made to obtain standard solutions of concentrations of 10, 25, 50, 75 and 100 µg/mL. The internal standard solution was prepared by dissolving 40 mg of propyl paraben in 100 mL methanol to provide a stock solution of 400 µg/mL. A constant volume (0. 5 mL) of that solution was added to 10 ml of each standard solution of ketoprofen. All solutions were filtered through 0.45 µm membrane filter prior to injection of 20 µL into the HPLC system (I). For constructing the standard calibration curves of the other two drugs, a standard solution of pseudoephedrine HCl in methanol (3.2 mg/mL) and another one of levocetirizine dihydrochloride in methanol (0.8 mg/ml) were prepared. Then, a stock standard solution of the two drugs was prepared by mixing 5 mL from each standard solutions and dilution up to 100 mL of methanol to provide stock concentrations of 160 µg/mL and 40 µg/mL of the two drugs, respectively. Serial dilution of this solution was made with sufficient quantity of methanol to produce 5 dilute solutions of concentrations of (100, 80, 50, 25, 12.5 µg/mL), (25, 20, 12.5, 6.25 and 3.125 µg/mL) of the two drugs, respectively. A stock solution of internal standard paracetamol in methanol (4 mg/mL) was prepared. A constant volume (0.25 mL) of that solution was added to 10 mL of the tested solution. All solutions were filtered through 0.45 µm membrane filter prior to injection of 20 µL into the HPLC system (II). In both systems, peak area ratio of each drug was determined by dividing the peak area of the drug by the peak area of internal standard. A calibration curve for each drug was constructed by plotting the drug concentrations versus the peak area ratio. The regression equation of each curve was determined and used thereafter to quantify the drug in a given sample.

To assay the drugs in each formulation, 100 ml of methylene chloride was added to the quantity of the effervescent powder (4 g), The mixture was shaken for 5 minutes and filtered. Both the filtrate and unfiltered residue were kept and analyzed. For Ketoprofen assay, the filtrate which contained only ketoprofen (due to its freely solubility in methylene chloride) was dried on air. The residue left was dissolved and made up to 100 ml of the mobile phase (system I). 10 ml of the solution was further diluted up to 100 ml with the same solvent .To 10 ml of the resultant solution, 0. 5 ml of internal standard solution was added. The solution was filtered through 0.45 µm membrane filter prior to injection of 20 µL into the HPLC system (I). For assay of Pseudoephedrine HCl and Levocetirizine dihydrochloride, the residue on the filter paper was washed with a 70 ml of methanol and filtered. The filtrate was made up to 100 mL with methanol. 20 mL of the solution was diluted up to 100 ml with methanol. To 10 mL of that solution, 0.25 mL of the internal standard solution was added. The solution was filtered through 0.45 µm membrane filter prior to injection of 20 µL into the HPLC system (II).

In both tests, the content of each drug was then determined as follows:

% Content=100 × Cp/Ct, where Cp and Ct were the practical and theoretical concentration of the drug, respectively.

Physical Characterization of the Powder

The powder characterization of each prepared formulation included determination of the powder density, flow ability and average particle size. The bulk density (Pb) was determined by pouring 100 g of the powder into a graduated cylinder (250 mL) using a glass funnel and the volume was then measured. The tapped density (Pt) was determined by tapping the cylinder containing the powder until on further volume changes occur [15]. Particle size analysis was determined by agitation of 25 g of the formulation powder for 10 min with a sieve shaker fitted with a progression of standard sieves [12]. The flowability of the powder was evaluated from the values of Hausner's ratio, Carr`s index and angle of repose. Hausner ration and Carr`s index were calculated as follows [9,16]:

Hausner ratio=Pt/Pb

Carr`s index=100 × (Pt-Pb)/P.t

The angle of repose (θ) was determined by allowing powders to flow through a funnel and fall freely onto a graph paper on a horizontal surface. The height (h) and radius (r) of the resulting cone were measured and the angle of repose was calculated from the following equation [16]:

tan θ=h/r.

Moisture Content

0.5 g of the powder (w1) was placed in an oven at 80°C for 4 hours. Then the weight after drying (w2) was measured. The moisture content was calculated from the following equation [17]:

Moisture content%=100 × (w1-w2)/w1.

Effervescent Time and pH

The effervescence time, which is the time required for a total effervescence of the powder, was measured by using stopwatch by placing 4 g of the powder in a beaker containing 50 mL of Water. The pH of the resulting solution was then measured immediately after completion of the effervescence using a pH meter [17].

Stage 2

***In vitro* drug release**

This stage involved estimation of the cumulative drug release% from the formulations selected from stage 1. The test was carried as described in the literature for effervescent tablets [9,18,19]. The dissolution was investigated in a medium of 500 ml phosphate buffer pH 6.8 using a USP II dissolution apparatus. The dissolution media was maintained at 37 ± 0.5°C and 50 rpm. Samples (5 mL) was taken after 5 minutes and analyzed for drug release of Ketoprofen since it is practically insoluble in water. The drug sample was extracted from the sample by four 30 mL methylene chloride. The collected organic layers were dried on air. The residue left was reconstituted and made up to 10 mL of the mobile phase (system 1), then 0.5 mL of internal standard solution (propyl paraben 400 µg/mL) was added. The solution was filtered through 0.45 µm membrane filter prior to injection of 20 µL was injected into the HPLC system 1.

Stage 3

Stability study

An isothermal accelerated stability study of only two formulations that demonstrated the highest drug release results in stage (2) was carried out. Samples, each of 4 grams, of the tested formulation were packaged in tightly closed aluminum foils and kept at refrigerator (4°C), incubator (37°C), and oven at (75°C). Analytical samples were taken at 0, 1, 3 and 6 weeks thereafter and the stability was evaluated in terms of physical appearance and drug content. The order of degradation reaction was determined by fitting drug content data versus time to zero, first and second orders models. The rate constants of degradation (K) of each drug at the stated storage condition were then determined and used to construct Arrhenius plot of (ln K) versus I/T ; where T was the temperature of storage in Kelvin [20]. The degradation rate (K25; weeks 1) at room temperature (25 oC)) was calculated from Arrhenius equation as follows

ln K25=(ln A)-[(Ea/R) * (1/T25)

where, (ln A) was the intercept in the plot and Ea/R=- slope

The predicted shelf-life (t90)was then calculated as follows:

t90 weeks=0.105/K25 ; for first order kinetic

t 90 (years)=t90 weeks /52.

RESULT AND DISCUSSION

Compatibility Study

Figure 1 shows the IR spectra reference standards of ketoprofen, pseudoephedrine HCl and Levocetirizine dihydrochloride compared to the spectrum of a physical mixture of the drugs with excipients. The spectrum of physical mixture demonstrated the same prominent peaks, at definite wavenumbers, that existed in the spectrum of the reference standard of each drug. This finding revealed proper drug-drug and drug-excipient compatibility.

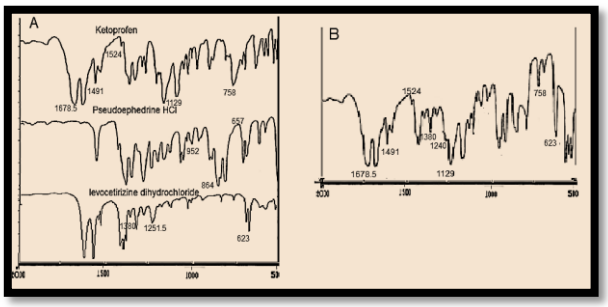


Figure 1: FT-IR spectra of (A): Reference standards of ketoprofen , pseudoephedrine HCl and Levocetirizine dihydrochloride , (B): physical mixture of the three drugs with excipients

Evaluation of the Formulations

Stage 1

Drug content: Figure 2 demonstrates the three standard calibration curves of ketoprofen and that of pseudoephedrine HCl and Levocetirizine dihydrochloride. The curves were linear with linearity of 0.9989, 0.9987 and 0.9927 for the three drugs, respectively. The regression equations of analysis of the three drugs were (y=0.0595x-0.0079), (y=0.00024x-0.0047) and (y=0.0039x-0.0069). As shown in Table 2, the average results of a triplicate testing of the content of the three drugs , respectively, in the 9 prepared formulations, ranged from (99.4 ± 2.5% to 102.2 ± 4.521%), (99.8 ± 6.721% to 103.6 ± 7.406%) and (99.1 ± 7.542% to 101.4 ± 3.443%). The perfect linearity of the three standard calibration curves, as well as the high values of drug contents (≥ 99%) determined for each drug, indicated optimum accuracy and appropriateness of the analytical techniques used.

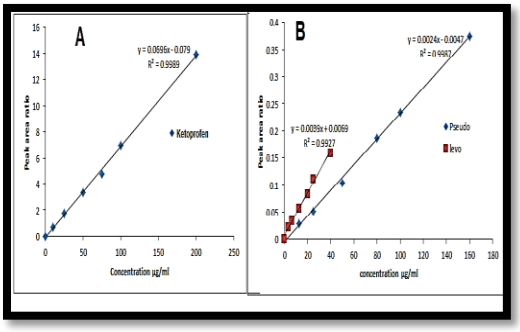


Figure 2: Standard calibration curve of HPLC analysis of ketoprofen (A) at 240 nm and of pseudoephedrine HCl and Levocetirizine dihydrochloride (B) at 210 nm

Table 2: Drug contents (%) of the three included drugs in the prepared effervescent formulations

Levocetirizine dihydrochloride	Pseudoephedrine HCl	Ketoprofen	Formulation Code
99.9 ± 8.112	99.5 ± 2.224	99.8 ±3.654	FM1
99.1 ± 7.542	101.3 ± 4.348	99.6 ±5.246	FM2
101.1 ± 2.256	102.7 ± 1.246	100.2 ± 7.121	FM3
100.7 ± 2.302	100.9 ±5.002	102.1 ± 9.101	FL1
99.6 ± 6.543	99.8 ± 6.721	102.2 ± 4.521	FL2
101.4 ± 3.443	99.9 ± 5.332	100.1 ± 5.55	FL3
100.4 ± 9.112	102.6 ± 7.112	101.4 ± 2.346	FS1
99.2 ± 6.125	103.8 ± 7.406	99.4 ± 2.5	FS2
99.7 ± 7.772	99.9 ± 9.012	99.5 ± 6.402	FS3

Powder characterization: As demonstrated in Table 3, the bulk density (g/mL) of the mannitol-included (FM), lactose-included formulations (FL) and starch-included (FS) formulations ranged from (1.02-1.12), (0.79-0.85) and (1.07-1.32), respectively. The larger bulk density of FM and FS formulations would predict that those formulations were better than FL formulations in terms of smaller pack volumes, more facilitated packing process and less problems of dust [14,16]. In addition, formulations FM and FS demonstrated Hausner ratio of <1.25, Carr`s index of <16 and angle of repose of <40, which indicated to the good flow properties of those formulations compared to poor flowability observed with FL formulations. Moreover, the average particle sizes of formulations FM (126.6-147 µm) and FS (129.8-137.2 µm)) were larger than those of FL formulations (111.2-120. 8 µm)) which could contribute to the good flow properties of the relevant formulations

Moisture content, effervescence time and pH of aqueous solution: Table 4 demonstrates the results of moisture content, effervescence time and pH of aqueous solution obtained from the 9 tested formulations. Because of the hygroscopic nature of effervescent base, the moisture content in the formulations with highest concentrations of effervescent base (FM3, FL3 and FS3) were greater than that in other formulations. Nevertheless, all formulations had moisture content of less than 1%. With respect to pH of aqueous solution, all formulations provided weak acidic pH with a range from 5.55 ± 0.121 to 5.74 ± 0.171. The effervescence times of all formulations were <60 seconds that time obviously decreased as the concentration of effervescence base increased. However, the shortest time (23 second) was recorded in both FM3 and FS3 formulations which contained 89.9% of effervescent base. Based on the results of stage 1 of evaluation, all FM and FS formulations (FM1, FM2, FM3, FS1, FS2, FS3) were selected to undergo stage 2 of evaluation.

Table 3: Physical characterization of powder formulations

	Density		Flowability			Average particle size (µm)
Code	**Bulk density**	**Tapped density**	**Hausner ratio**	**Carr`s index**	**Angle of repose (º)**	
	(g/mL)	**(g/mL)**		**%**		
FM1	1.02 ± 0.007	1.21 ± 0.34	1.19 $^{\Delta}$	15.7 $^{\square}$	24.2 ± 1.034	126.6 ± 11.523
FM2	1.05 ± 0.054	1.26 ± 0.012	1.18 $^{\Delta}$	15.08 $^{\square}$	26.5 ± 2.056	135.5 ± 9.724
FM3	1.12 ± 0.032	1.31 ± 0.057	1.17 $^{\Delta}$	14.50 $^{\square}$	28.7 ± 0.983	147.1 ± 13.211
FL1	0.79 ± 0.006	1.33 ± 0.033	1.68	40.6	47.6 ± 3.236	111.2 ± 4.345
FL2	0.81 ± 0.012	1.29 ± 0.045	1.59	37.21	45.2 ± 1.005	117.6 ± 7.721
FL3	0.85 ± 0.025	1.39 ± 0.022	1.64	38.85	44.1 ± 2.346	120.8 ± 2.245
FS1	1.07 ± 0.52	1.19 ± 0.013	1.11 $^{\Delta}$	10.08 $^{\square}$	22.5 $^{\Diamond}$ ± 1.025	129.8 ± 8. 124
FS2	1.22 ± 0.011	1.35 ± 0.033	1.11 $^{\Delta}$	9.63 $^{\square}$	24.2 $^{\Diamond}$ ± 0.761	136.3 ± 6.611
FS3	1.32 ± 0.037	1.41 ± 0.015	1.07 $^{\Delta}$	6.38 $^{\square}$	28 $^{\Diamond}$ ± 0.45	137.2 ± 5.317

Δ, □ , ◊: Good flowability, Δ: < 1.25, □: ≤ 16 , ◊: (20-30).

Table 4: Moisture content, effervescence time and aqueous solution pH of formulations

pH of aqueous solution	Effervescence time (sec.)	Moisture content%)	Formulation Code
5.71 ± 0.394	39 ± 3.124	0.35 ± 0.015	FM1
5.68 ± 0.146	31 ± 1.308	0.4 ± 0.024	FM2
5.55 ± 0.121	23 ± 1.246	0.45 ± 0.011	FM3
5.74 ± 0.171	45 ± 4.002	0.34 ± 0.001	FL1
5.66 ± 0.221	41 ± 2.221	0.39 ± 0.005	FL2
5.57 ± 0.05	37 ± 1.113	0.43 ± 0.012	FL3
5.73 ± 0.111	37 ± 3.12	0.36 ± 0.013	FS1
5.62 ± 0.42	30 ± 1.008	0.38 ± 0.021	FS2
5.56 ± 0.322	23 ± 1.023	0.41 ±0.013	FS3

Stage 2: *In vitro* drug release

In this stage, the release of ketoprofen release from 6 formulations was investigated.
As demonstrated in Table 5 and Figure 3, the cumulative drug release increased as the concentration of effervescent base increased which could be attributed to the impact of effervescent base concentration in drug dissolution. FM formulations showed cumulative drug release after 5 minutes, ranging from 94.7 (from FM1) to 99.7% (from FM3), while that from FS formulations ranged from 98.2% (from FS1) to 100.1%) from FS3. Accordingly, only two formulations (FM3 and FS3) could release approximately 100% of the drug. Therefore, these 2 formulations were selected to undergo the last stage of evaluation.

Table 5: Cumulative *in vitro* release of Ketoprofen from different effervescent powder formulations

Formulation code						Time (Min)
Cumulative drug release% of Ketoprofen						
FS3	FS2	FS1	FM3	FM2	FM1	
96.7	95.3	94.2	96.3	93.1	91.5	2
100.1	96.6	98.2	99.7	96.5	94.72	5
100.1	97.3	98.3	99.7	97.5	94.82	7
100.1	99.3	99	99.9	98.2	95.92	10

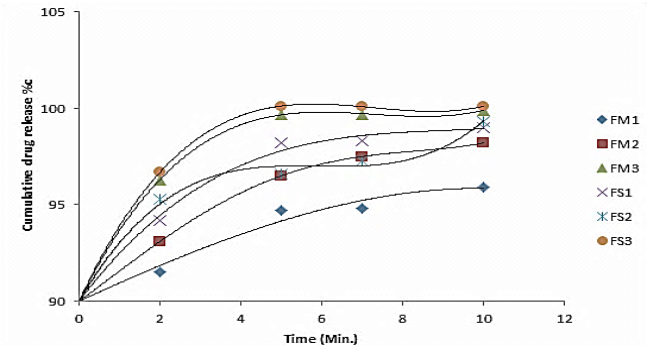


Figure 3: In vitro drug release of Ketoprofen from different effervescent powder formulations

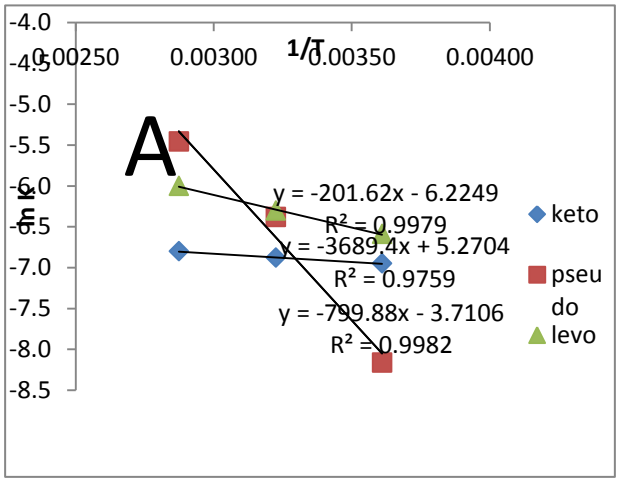
Stage 3

Stability study: The isothermal accelerated stability study was performed on 2 formulations (FS3 and FM3) that demonstrated better dissolution in stage 2. The study was carried out in 6 weeks at 3 different storage temperatures (4, 37 and 75°C). The two formulations showed no changes in physical appearance in the three conditions along that period.

Concerning, the changes in drugs content, the degradation reactions of the three drugs in each storage condition obeyed the first-order model of kinetics. The determined degradation rate constant (K) at each condition for each drug was determined and used to construct Arrhenius plot of (ln K) versus (1/T). As shown in Figure 4 and Table 6, the plots of all drugs at each storage condition were linear with a square of correlation (r2) of not less than 0.98. The rates of degradation (expressed as K25 in weeks 1 of ketoprofen, pseudoephedrine HCl and levocetirizine dihydrochloride in FM3 were 0.001, 0.0008 and 0.0017 weeks 1 , respectively,, while in FS3 formulations , the rates were 0.0014, 0.0013 and 0.0036 weeks 1, respectively. This finding showed that in FS3, the degradation rates of drugs were obviously slower than those in FM3. In both FM3 and FS3, levocetirizine dihydrochloride demonstrated the shortest shelf-life (t90) than the other two drugs. However, in FS3 , that shelf-life (1.2 years) was approximately 2 folds longer than that in FM3 formulation.

Table 6: Results of isothermal Accelerated stability study using Arrhenius plot (ln K versus 1/T) of formulations FS3 and FM3

Parameters	FS3			FM3		
	Ketoprofen	Pseudoephedrine HCl	Levocetirizine dihydrochloride	Ketoprofen	Pseudoephedrine HCl	Levocetirizine dihydrochloride
Slope (Ea/R)	-201.622	-5.27	-799.877	-1664.977	-5270.802	-1007.129
Intercept (ln A)	-6.225	5.27	-3.711	-0.967	11.006	-2.255
(R^2) ▲	0.998	0.976	0.998	0.999	0.982	0.981
k_{25} (weeks^{-1})	0.001	0.0008	0.0017	0.0014	0.0013	0.0036
t_{90} (years)	2.007	2.475	1.209	1.419	1.613	0.565



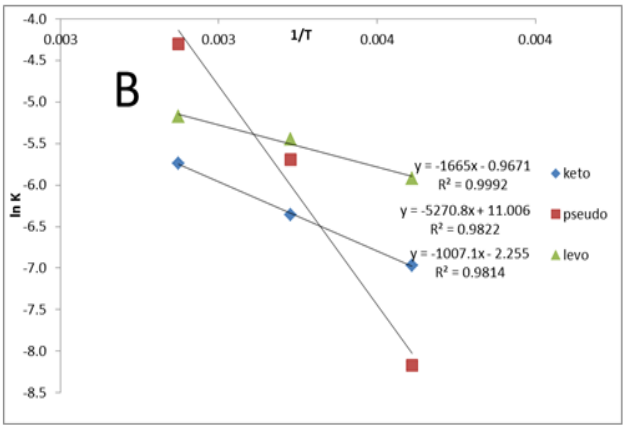


Figure 4: Arrhenius plot of isothermal stability study of (A) formulation FS3, and (B) formulation FM3.

CONCLUSION

Based on the results obtained from this study, it could be concluded that the effervescent powder formulation containing starch as a diluent and 89.9% effervescent base can be a novel common cold combination of ketoprofen 50 mg, pseudoephedrine HCl 60 mg and levocetirizine dihydrochloride 2.5

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