doi.org/10.36721/PJPS.2023.36.1.SP.247-254.1

Design, formulation, optimization and stability studies of paracetamol effervescent tablets

Danish Hassan Dani[1], Syed Baqir Shyum Naqvi[1], Muhammad Akram[2], Sheikh Abdul Khaliq[3]* and Muhammad Iqbal Nasiri[4]

[1]Department of Pharmaceutics, Faculty of Pharmacy, Hamdard University, Karachi, Pakistan
[2]Research and Development Department, Barrett Hodgson Pakistan (Pvt) Ltd, S.I.T.E, Karachi, Pakistan
[3]Department of Pharmacy Practice, Faculty of Pharmacy, Hamdard University, Karachi, Pakistan
[4]Faculty of Pharmacy, Hamdard University, Islamabad Campus, Pakistan

Abstract: The purpose of the current study was to develop stable effervescent-tablets without controlling area relative-humidity; temperature and no requirement of special packaging. Current 3^2 factorial-design experimental studies were conducted in the Research Laboratory of Pharmaceutics, Hamdard University. Duration of study is from December-2021 to November-2022. Various paracetamol based effervescent formulations (F1-F9) were prepared with different molar-ratio of citric-acid anhydrous and sodium-bicarbonate as independent variables. Design-Expert® software was used to graphically express the influence of each factor. By novel approach; tablets were compressed at ambient temperature and relative-humidity; acid components were kept on one-side and basic ingredients on another side; both sides were separated by an inert-layer. Tablets were kept at accelerated humidity and temperature in normal packing for six months; after six months, F6 formulation was found acceptable based on effervescence-time (120 sec), pH-value (5.5) and other quality criterion. Parameters of assay, effervescence-time, pH-value and carbon-dioxide content were found within the set-limit. Hence; novel approach for developing effervescent formulation by separating acid components at one-side and basic ingredients on another side of tablet through inert-layer is workable under room temperature and humidity. It is expected that commercial production of tablets by this technique may reduce cost of effervescent products and no requirement for special packaging.

Keywords: 3^2 factorial design, novel, cost-effective, special packaging, rapid disintegrating.

INTRODUCTION

Oral route of drug administration has always been preferred; it is a natural route of administration having better patient compliance among most of systemic routes (Homayun *et al.*, 2019). Oral administration of solid and liquid dosage forms is instrumental to get required results without any trouble (Hua, 2020). Solid oral medications are one of the unique formulations of drug; however, there are some drawbacks like slow absorption of API (Active Pharmaceutical Ingredient), absorption can be improved by administering the drug in the form of liquid. Due to this reason; drug delivery has its own importance in health care system and it can get excellent outcomes (Davoodi *et al.*, 2018). Despite advancement in pharmaceutical technologies; biggest challenge is keeping the pharmaceutical product stable from environmental harms.

Effervescent tablets have more merit points than many other conventional dosage forms; it is used in fluid-form; having no swallowing issues; better effects on patient's stomach and appealing nature of tablets can make the marketing for this product very easy (Korde *et al.*, 2021). Another advantage of effervescent dosage form is that the whole formulation reaches to the stomach. Similarly, effervescence system has better pharmacokinetic absorption compared to conventional dosage form (Kim *et al.*, 2018). Controlled manufacturing area has much significance in dealing with effervescent systems. Considering the preparation which is easily affected by humidity and temperature; the RH (Relative Humidity) and temperature must be lower than or equal to 25% and 25°C respectively; such conditions prevents moisture absorption and ultimately no clumping, no sign of tablet sticking with machinery (Samiei *et al.*, 2017). The high price, stability of these formulations and approximated shelf life are the biggest issues. For regulatory compliance; these formulations must be guaranteed for the stability requirements during transit and storage (Haider *et al.*, 2020). There are some complexities in controlling the atmospheric conditions particularly RH and temperature. In addition; to avoid unwanted effervescent reaction between acidic and basic medium during production; specialized package is also required to maintain product stability throughout its shelf-life.

Therefore; the primary objective of study was to design, formulate and optimize effervescent system after addressing RH and temperature. Secondary objective was to determine its shelf-life. Paracetamol (PCM) was taken as a model drug; its usage can be seen in each and every

*Corresponding author: e-mail: sheikh1974@gmail.com

part of the world for acute or chronic pain (McCrae *et al.*, 2018).

MATERIALS AND METHODS

Study design, place and duration

Current 3^2 factorial-design experimental studies were conducted in the Research Laboratory of Pharmaceutics, Hamdard University, located in cosmopolitan city of Pakistan; Karachi. Design Expert® software (version-12, Stat-Ease, Inc, USA) was used in order to graphically express the influence of each factor ("Design-Expert® software, version 12, Minneapolis, MN, USA," 2022). Duration of study is from December-2021 to November-2022.

Study objectives

Primary objective of study was to design, formulate and optimize effervescent system after addressing RH and temperature. Secondary objective was to determine its shelf-life and economy for pharmaceutical industry.

Materials

Paracetamol, pregelatinized starch, mannitol, citric-acid anhydrous, sodium-bicarbonate, crospovidone, polyethylene-glycol 6000 (PEG 6000) and sucralose, coloring, sweetening and flavoring agents. Analytical grade chemicals were used. Among main components; citric acid is a very important commercial product, 70% of food industry, 12% of pharmaceutical industry and remaining 18% use by other industries.(Igliński *et al.*, 2022) Citric acid is a weak tricarboxylic acid; the pKa values of its three carboxylate are 3.15, 4.78 and 6.40 respectively.(Lambros *et al.*, 2022) On the other hand Sodium-bicarbonate was use as an effervescence agent. According to US-FDA, when sodium-bicarbonate and citric acid mix together; react rapidly in water and release CO_2; release of CO_2 enhances the dissolution of active pharmaceutical ingredient.(Lodhi *et al.*, 2022)

Packaging material of effervescent system

There are some complexities in controlling the atmospheric conditions particularly RH and temperature; which degrade effervescent product. During manufacturing; product should be protected from unwanted effervescent reaction between acidic and basic medium; specialized package is also required to maintain product stability throughout its shelf-life, which further increases the cost of product.

Experimental procedure

Factorial design of experiment

In this study, a 3^2 factorial design was used to optimize the formulation. Design Expert® software (version-12, Stat-Ease, Inc, USA) was used in order to graphically express the influence of each factor ("Design-Expert® software, version 12, Minneapolis, MN, USA," 2022). Two factors such as sodium-bicarbonate (X_1) and citric-acid anhydrous (X_2) were used at three levels of molar concentration; i.e., 5, 6 and 7 moles of sodium-bicarbonate and 1.5, 2 and 2.5 moles of citric-acid anhydrous as an independent variable; whereas, effervescence time (Y_1) and pH value (Y_2) were selected as dependent variables (table 1).

Preparation effervescent granules

Initially; paracetamol and pregelatinized starch were mixed, wet granulated with purified water and then passed through sieve number 40. The wet granules are dried until moisture contents are less than 1%, it is further followed by dry sieving using the same sieve number. Dried granules were divided into two portions, one portion was mixed with sodium-bicarbonate and half quantities of mannitol, crospovidone, polyethylene glycol 6000, while second portion was mixed with citric-acid anhydrous and remaining half quantities of mannitol, crospovidone, PEG-6000. Compositions of all formulations (F1-F9) are listed in table 2.

Pre-compression evaluation of granules blend

For evaluation, the particle size distribution was determined by using vibration sieve shaker (ERWEKA, AR-402) set with sieve number 20-120; through which granules were passed (Kumaravelrajan *et al.*, 2022). The percentage retained on each sieve and mean particle size were determined. The prepared granules blend were evaluated for moisture constituents by moisture analyzer (Radwag MA 210.R) (Żołek-Tryznowska *et al.*, 2021). The bulk density, tapped density, compressibility index, hausner's ratio and angle of repose (Xu *et al.*, 2019) were also determined by following equations, respectively as reported previously:-

$$\text{Bulk density} = \frac{M}{V_o} \quad (1)$$

$$\text{Tapped density} = \frac{M}{V_f} \quad (2)$$

$$\text{Carr's index} = \left(\frac{V_o - V_f}{V_o}\right) \times 100 \quad (3)$$

$$\text{Hausner's Ratio} = \frac{V_o}{V_f} \quad (4)$$

$$\theta = \tan^{-1}\left[\frac{h}{r}\right] \quad (5)$$

Where; V_o = initial volume in mL; M = mass in gram; V_f = final volume samples after tapping in mL; θ = angle of repose; h = height of powder cone and r = radius of the powder cone. If Carr's index is less than 10; powders show excellent flow properties. Angle of repose value lies in between 25-30 and Hausner's ratio lies in between 1.00- 1.11 (USP, 2021).

Preparation of effervescent tablets and post-compression evaluation

Both parts (acidic and alkaline blend) of formulations were compressed in the form of multi-layered tablets,

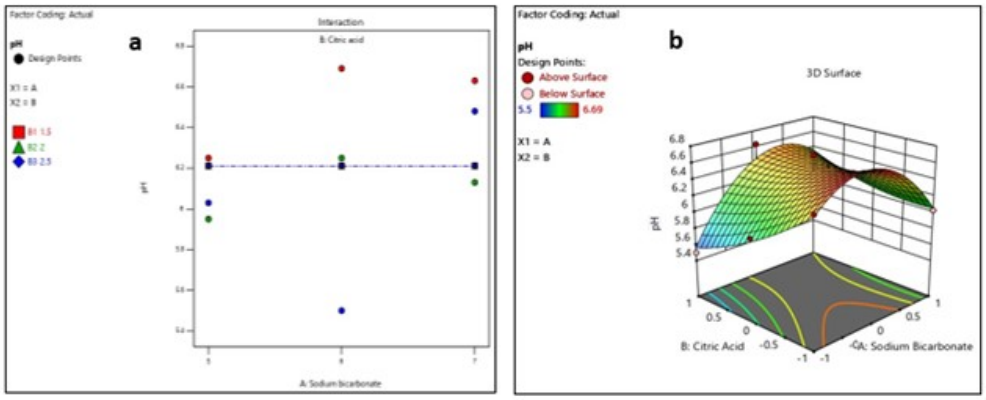

Fig. 1: (a) scatterplot showing effect of interaction of independent variables on pH response, (b) 3D response surface graph showing effects of independent variables on pH response

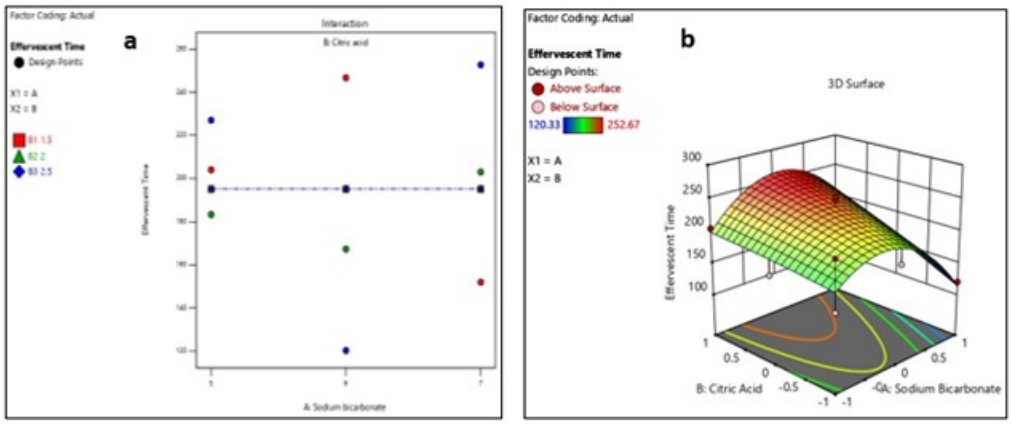

Fig. 2: (a) scatterplot showing effects of interaction of independent variables on effervescent time; (b) 3D response surface graph showing effect of independent variables on effervescent time response

while keeping a thin layer of diluent in between the two parts. The developed tablets were characterized for various parameters such as weight variation (Sunand *et al.*, 2017) and hardness (Copley TBF, 1000) (Maclean *et al.*, 2021) as per USP (United States Pharmacopeia). The disintegration time (effervescent time) of the tablets was also determined; a beaker is taken, 200ml purified water was added and then tablet was placed in the beaker followed by mixing the content for 5 seconds (Taymouri *et al.*, 2019); immediately after completion of effervescent reaction; pH-value of the solution was checked by using pH meter (Martini). For the evaluation of CO_2 content in each tablet, a beaker containing 100ml of 1N sulfuric-acid solution was placed on weighing balance, tarred and followed by addition of one tablet; weight changes were noted after completion of chemical reaction. The obtained weight at the end of chemical reaction was subtracted from initial weight; difference in weight showed the amount of CO_2 in mg per tablet (Aslani & Jahangiri, 2013). To perform assay, standard stock solution was prepared. Initially; 100mg of Paracetamol was weighed; dissolved in 10ml of methanol; diluted with 500ml purified water and mixed well. 5ml stock solution was taken and diluted with 100 ml purified water to make standard concentration of 10mcg/ml. For working solution (sample); 10 tablets of each formulation were weighed and grinded to make fine powder. Grinded powder (approx. 380 mg) was taken equivalent to 100mg paracetamol; dissolved in 10ml methanol; diluted with 500 ml purified water and mixed well. 5ml solution was taken and diluted with 100ml purified water to make sample solution. Absorbance of both standard and sample solutions was measured at 243nm using a spectrophotometer. The percentage assay was calculated by using the following equation:

$$\%\text{Assay} = \left[\frac{\text{Absorbance of Sample}}{\text{Absorbance of Standard}}\right] * 100 \quad (6)$$

Stability study

The stability study was conducted as per the International Council for Harmonization (ICH) guidelines (González-González *et al.*, 2022). Optimized formulation (F6-3) was primarily wrapped in aluminum sheet, followed by packed in polyvinyl chloride bottle and kept on accelerated temperature of 40°C±2°C & 75±5% relative-humidity. After a predetermined time period of 3 months and 6 months; samples were taken out from the packing and performed assay, disintegration time, pH-value and carbon-dioxide (CO_2) contents.

STATISTICAL ANALYSIS

Statistical analysis was done by Statistical Package for Social Sciences (SPSS) 22 version.

RESULTS

Factorial design, analysis and optimization of formulation

Results of experimental design batches (F1 to F9), independent variables (X_1 and X_2), their levels values (0, 1 and -1) and combinations of coded molar values, are mentioned in table 1. Response surface plot for pH-values and effervescent time are given in fig. 1-2. fig. 1a (scatter-plot) shows the quantities of sodium-bicarbonate and citric-acid in molar concentrations at three different levels; pH increases in most of cases with the increase in molar concentrations of sodium-bicarbonate; decreases with the increase in molar concentrations of citric-acid anhydrous with a few deviations. fig. 1b contains pH response 3D surface graph. The optimized formulation (F6-3) showed pH value of 5.50±0.02. fig. 2a (scatter-plot) shows the quantities of acid and base in terms of number of moles used, where 3 different colors indicate quantities of acid, while the quantities of base are mentioned on X-axis and effervescent time response is mentioned on Y-axis. Varied combinations of acid and base in different quantities will yield different effervescent time and 3D surface graph of effervescent time is mentioned in fig. 2b. The equation for factorial design is mentioned below:-

$$Y=(b)+(b_1 X_1)+(b_2 X_2)+(b_{12}X_1X_2)+(b_{11}X_1^2)+(b_{22}X_2^2) \quad (7)$$

Pre-compression evaluation

Mean particle size distribution of the powder blends: 0.131mm-0.220mm. table 3 shows bulk densities, tapped densities, moisture content, Hausner's ratio, Carr's index and angle of repose of all formulations.

Post-compression evaluation

Uniformity of weight test of tablets was within the described USP specification of ±5%. Hardness of all formulations was found 5.27±0.21-6.17±0.06kg/cm^2. Disintegration time was found within the acceptable limit (152.0±2.65-252.67±3.06 seconds). The CO_2 content in were found to be in the range (221.33±2.08 to 327.0±2.0 mg). The pH of tablet solution were found in the range (5.95±0.01-6.69±0.01). The percent assay of paracetamol was found within the defined limit (99.47±0.55-100.93±0.38%) (table 4).

Table 1: 3^2 Factorial design layouts, independent variables and their levels

Formulation Code	X_1	X_2
F1	-1	-1
F2	-1	0
F3	-1	1
F4	0	-1
F5	0	0
F6	0	1
F7	1	-1
F8	1	0
F9	1	1
Level	Molar concentration of sodium bicarbonate (X_1)	Molar concentration of citric acid anhydrous (X_2)
-1	5.0	1.5
0	6.0	2.0
1	7.0	2.5

Note: Disintegration time/ Effervescent time (Y_1) and pH value (Y_2) are dependent variables

Table 2: Compositions of all formulations (F1-F9).

Ingredients	Amount per tablet (mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Paracetamol	500	500	500	500	500	500	500	500	500
Sodium Bicarbonate	420	420	420	504	504	504	588	588	588
Citric Acid Anhydrous	288	384	480	288	384	480	288	384	480
Mannitol	572	476	380	488	392	296	404	308	212
Pregelatinized Starch	50	50	50	50	50	50	50	50	50
Crospovidone	50	50	50	50	50	50	50	50	50
Polyethylene Glycol 6000	20	20	20	20	20	20	20	20	20
Total weight per Tablet	1900	1900	1900	1900	1900	1900	1900	1900	1900

Table 3: Characterization of effervescent granules

Formulation Code	Angle of Repose (θ^0)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index (%)	Hausner's Ratio	Moisture Content (%)
F1	26.5±0.40	0.81±0.01	0.89±0.01	8.27±0.125	1.09±0.01	1.30±0.05
F2	29.57±0.35	0.78±0.01	0.88±0.01	11.36±1.07	1.13±0.01	1.31±0.03
F3	32.40±0.44	0.85±0.01	0.95±0.01	10.87±1.12	1.12±0.01	1.33±0.04
F4	33.50±0.40	0.87±0.01	0.99±0.01	11.82±1.49	1.13±0.02	1.22±0.09
F5	34.50±0.40	0.74±0.01	0.85±0.01	13.28±0.73	1.15±0.01	1.56±0.04
F6	27.90±1.80	0.76±0.01	0.84±0.01	9.12±0.60	1.10±0.01	1.12±0.02
F7	29.60±0.44	0.83±0.01	0.91±0.01	9.15±1.58	1.10±0.02	1.26±0.04
F8	34.47±1.01	0.74±0.01	0.86±0.01	13.23±0.63	1.15±0.01	1.24±0.05
F9	29.53±0.25	0.80±0.01	0.88±0.01	9.08±1.89	1.10±0.02	1.53±0.02

All values are expressed as mean ± SD

Table 4: Physical and chemical parameters of effervescent formulations

Formulation Code	Weight variation* (mg)	Hardness* (Kg/cm^2)	Disintegration Time (sec)	CO_2 Content (mg)	pH of Solution	Assay (%)
F1	1906.20±3.79	5.27±0.21	204.0±3.61	229.33±1.53	6.25±0.1	100.70±0.53
F2	1908.50±2.89	5.50±0.40	183.33±2.89	221.33±2.08	5.95±0.01	99.47±0.55
F3	1907.50±3.51	6.17±0.06	227.0±2.0	228.0±2.0	6.03±0.02	100.42±0.68
F4	1906.10±4.73	5.90±0.20	246.67±2.08	276.0±1.73	6.69±0.01	99.50±0.40
F5	1910.60±2.65	5.33±0.21	167.33±2.08	288.67±3.21	6.25±0.01	100.09±0.18
F6	1909.40±1.53	6.02±0.10	120.33±2.08	280.67±0.58	5.50±0.02	100.07±0.15
F7	1908.80±4.04	5.50±0.40	152.0±2.65	327.0±2.0	6.63±0.02	100.93±0.38
F8	1905.50±4.04	5.50±0.40	203.0±2.65	302.67±2.52	6.13±0.02	100.28±0.80
F9	1908.60±3.51	5.37±0.38	252.67±3.06	295.67±2.08	6.48±0.24	99.90±1.06

*All values are expressed as mean ± SD, n = 20

Table 5: Stability study data of optimized formulation (F6-3)

Parameters	Initial results	After 3 months	After 6 months
Assay (%)	100.1	99.9	100.2
Effervescent Time (sec)	120	125	130
pH of solution	5.5	5.54	5.42
CO_2 Content (mg)	280	278	275

Stability study

Formulation F6-3 has proved stable in the accelerated stability study up to 6 months at a temperature of 40°C±2°C and relative humidity 75%± 5% (table 5).

DISCUSSION

Factorial design study is a kind of an experimental design; widely used to conduct research and develop pharmaceuticals; it is easy, understandable and self-explanatory (Cheng, 2016). In order to optimize the amount of citric-acid anhydrous and sodium-bicarbonate; a 3^2 factorial experimental design was applied; purpose of this design was to obtain faster disintegration and release of higher amount of carbon-dioxide as well as drug in few seconds. CO_2 is released when the acid and base reaction occurs at the time they come in contact with each other in the presence of water (Kim *et al.*, 2018). fig. 1a shows the quantities of sodium-bicarbonate and citric-acid in molar concentrations at three different levels; where pH increases in most of the cases with the increase in molar concentrations of sodium-bicarbonate, nevertheless; decreases with the increase in molar concentrations of citric-acid anhydrous with few deviations. fig. 1b contains pH response 3D surface graph. Once the stoichiometric reaction is completed; the remaining excipients would impact many formulation properties of the Paracetamol, including solubility and pH; sodium-bicarbonate has the ability to modify pH of a solution (Wang *et al.*, 2019), obviously citric-acid will also influence pH of the formulation at the time of administration. Solution pH as an important parameter; helps in maintaining the taste of the formulation; also have effects on drug penetration (Joshi *et al.*, 2012) and the pH lesser than 6 will aid the formulation for better absorption (Kim *et al.*, 2018).

In the current study; the optimized formulation (F6-3) showed pH-value of 5.50±0.02. fig. 2a shows the

quantities of acid and base in number of moles; 3 different colors indicate quantities of acid; quantities of base are mentioned on X-axis and effervescent time response is mentioned on Y-axis. Various combinations of acid and base in different quantities will yield different effervescent time and 3D surface graph (fig. 2b). Effervescent time must be lesser than 3 minutes (Thoke *et al.*, 2013) and should be able to attain better patient compliance. Fortunately in the current study; optimized formulation (F6-3) showed least time of 120.33±2.08 seconds for completion of reaction. Topping up the quantities of acid and base can cause escalation in effervescent reaction; which may reduce the time needed to complete effervescence. The PEG-6000 can cause the effervescent time to increase and may harden the tablet which can delay disintegration (Taymouri *et al.*, 2019). Due to this reason; PEG-6000 was kept constant in all of the formulation with very less quantity.

Due to many environmental factors; particularly humidity and temperature; premature reaction can take place which can lead to unwanted carbon-dioxide production; making the product unstable; thus a controlled environment (25% RH at 25ºC or less) is required (Chuong *et al.*, 2018). Environmental moisture absorption is the substantial drawback for effervescent products, therefore; a need of trailblazing production technology is needed to protect products from degradation (Pagire *et al.*, 2020). Packaging material for effervescent tablet must save the tablet from different external factors like shear and trapped air; which can cause harm and physical degradation of tablets (Ali *et al.*, 2022). Delicate aluminum packaging is used; however; it raises the cost of product (İpçi *et al.*, 2016). In the current study; environmental risks for effervescent tablets were addressed by using a novel production technique, in which an acid and base component were kept apart by using a fine layer of diluent; which minimize the risks of any accidental effervescent reaction. Benefits of current novel technique are; omission of the need of control humidity, other environmental factors and special packaging requirement, less production of cost. Normally, there is no need of disintegrants in case of effervescent formulations, however; in the current study disintegrating agent was used to ensure the dispersion and disintegration of tablet smoothly.

Regarding the physical parameters of formulation; mean particle diameter was found to be 0.131mm-0.22mm. Material bulk properties and their flow depend on particles size, as the particle size grow owing to curtailment of inter particle bonds and the removal of fines will result in fall of bulk density (Shi *et al.*, 2018). Moisture content of granules can also affect the flowability of particles; powders having 20% or more moisture shows least flowability (Tannous *et al.*, 2013). Formulation prepared in current study will not have any issue of flowability because the moisture content of all formulations of current study was found in between 1.12±0.02% to 1.56±0.04%. Another physical parameter is Hausner's ratio of powders; it's value should be less than 1 to show an excellent flow; if value is greater than 1, then the flowability will be decreased. In the current study, all formulations indicated good flowability, because values of the Hausner's ratio were found in between 1.09±0.01 and 1.15±0.01. Similarly for Carr's index, if the value is lesser than or equal to 10; the powder will be considered having excellent flowability; if the powder having value of 38 or more; considered having very poor flow or even not flowable. The values of Carr's index of all formulations were found in between 9.08±1.89 and 13.28±0.73; showing good flow characteristics. Angle of repose is another parameter that impact on flowability of powder; such as impact on density, packing ability, internal friction and strength of the same material (Al-Hashemi *et al.*, 2018). It has a value in between 0° to 90° but mostly used up to 40°. The angle of repose of all formulations was found to be in range of 26.5°±0.40 to 34.50°±0.40; indicating good and passable flow c haracteristics.

Another imperative parameter is uniformity of weight; the USP specifies the range of ±5%; all formulations were found within the described USP specification. Tablets also need to show strength against break during handling, warehousing and transportation; strength of tablets can be counted as hardness ($Kg/cm^{2)}$ (Patel *et al.*, 2018). Satisfactory results of tablet hardness were obtained of all formulations; values were observed in the considerably acceptable range of 5.27±0.21 to 6.17±0.06 (Kg/cm^2). The disintegration time was found within the acceptable limit of all formulations i.e. 152.0±2.65 to 252.67±3.06 seconds. The CO_2 content will effect the taste (Aslani & Eatesam, 2013), the release of CO_2 will depend on the the extent of completion of effervescent reaction. The CO_2 content in all formultions were found to in the range of 221.33±2.08 to 327.0±2.0mg. Similarly; the pH of tablet solution were found in the range of 5.95±0.01 to 6.69±0.01. The percentage assay of drug must be within the limits of ±10% (USP, 2021). The percent assay of paracetamol in each formulation was found within the defined limit of 99.47±0.55-100.93±0.38%; hence showing uniformity of drug content.

CONCLUSION

It is possible to formulate and optimize paracetamol effervescent system after addressing RH and temperature. Novel approach for developing stable effervescent formulation by separating acid components at one side and basic ingredients on another side of tablet through inert-layer is workable under room temperature and humidity. It is expected that commercial production of tablets by this technique may reduce cost of effervescent products and no requirement for special packaging.

ACKNOWLEDGEMENTS

Authors acknowledge the research support of; M/S Zenith Pharmaceuticals, Pakistan for providing the gift sample of drug (Paracetamol); Merck, Pakistan for providing pregelatinized starch, mannitol, citric acid anhydrous, sodium bicarbonate, crospovidone, polyethylene glycol 6000 (PEG 6000) and sucralose; Allied Impex, Karachi for providing coloring, sweetening and flavoring agents. The authors are also thankful to Prof. Dr. Kamran Zaheer, Professor and Head of Department - Pharmaceutics, Hamdard University, for providing laboratory facilities, equipment, and his valuable guidance and Dr. Tariq Ahmed for support and cooperation. Authors also acknowledge for research support of Dr. Iyad Naeem Muhammad, Associate Professor and Head of Department of Pharmacy Practice, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Karachi, Pakistan.

REFERENCES

Al-Hashemi HMB and Al-Amoudi OSB (2018). A review on the angle of repose of granular materials. *Powder Techn.,* **330**(1): 397-417.

Ali F and Khan I (2022). Pharmaceutical Packaging. *In*: Khan SA (Ed.), Essentials of Industrial Pharmacy Springer, Cham: Springer. **46**(1): 55-66.

Aslani A and Eatesam P (2013). Design, formulation and physicochemical evaluation of acetaminophen effervescent tablets. *J. Reports Pharmaceut. Sci.,* **2**(2): 140-149.

Aslani A and Jahangiri H (2013). Formulation, characterization and physicochemical evaluation of ranitidine effervescent tablets. *Adv. Pharmaceut. Bull.,* **3**(2): 315.

Cheng CS (2016). Factorial Treatment Structure and Complete Factorial Designs, Chapter 6, Theory of Factorial Design: CRC Press, Taylor & Francis Group, 6000 Broken Sound Parkway NW, Suite 300.

Chuong MC, Kelley CJ, Muhammad Y, Caputo TD, Gomes JM, Oliveira D and Vazquez C (2018). Investigating effect of water of hydration on active pharmaceutical ingredients in a water-sensitive dosage form. *J. Analyt. Sci. Techn.,* **9**(1): 1-8.

Davoodi P, Lee LY, Xu Q, Sunil V, Sun Y, Soh S and Wang CH (2018). Drug delivery systems for programmed and on-demand release. *Adv. Drug Del. Reviews,* **132**(1):104-138.

Design-Expert®, V-12, Minneapolis, MN, USA (2022). www.statease.com

González-González O, Ramirez IO, Ramirez BI, O'Connell, P, Ballesteros MP, Torrado JJ and Serrano DR (2022). Drug Stability: ICH versus Accelerated Predictive Stability Studies. *Pharmaceutics,* **14**(11): 2324-2344.

Haider K, Akash MSH, Faheem A and Rehman K (2020). Guidelines for Drug Stability and Stability Testing. *In*: Akash MSH and Rehman K (Eds.). Stability Testing of Pharmaceutical Products. Singapore: Springer Singapore. **1**: 19-29.

Homayun B, Lin X and Choi HJ (2019). Challenges and recent progress in oral drug delivery systems for biopharmaceuticals. *Pharmaceutics,* **11**(3): 1-29.

Hua S (2020). Advances in oral drug delivery for regional targeting in the gastrointestinal tract-influence of physiological, pathophysiological and pharmaceutical factors. *Front. Pharmacol.,* **11**(1): 1-22.

Igliński B, Kiełkowska U and Piechota G (2022). Proecological aspects of citric acid technology. *Clean Techn. Environ. Policy,* **24**(7): 2061-2079.

İpçi K, Oktemer T, Birdane L, Altıntoprak N, Muluk N B, Passalı D and Lopatin A (2016). Effervescent tablets: A safe and practical delivery system for drug administration. *ENT Updates,* **6**(1): 46-50.

Joshi H, Dyade G and Patil R (2012). Effect of solubility enhancers on the solubility of paracetamol. *Indo-Am. Pharmaceut. Res.,* **3**(1): 1387.

Kim S, Hwang KM, Park YS, Nguyen TT and Park ES (2018). Preparation and evaluation of non-effervescent gastroretentive tablets containing pregabalin for once-daily administration and dose proportional pharmacokinetics. *Int. Pharmaceut.,* **550**(1-2): 160-169.

Korde AB, Waghmare SN, Bote SS, Palekar RS and Ghumre PB (2021). Formulation and evaluation of paracetamol effervescent tablet. *World J. Pharmaceut. Res.,* **10**(8): 1062-1072.

Kumaravelrajan R, Raj VM, Thirumaran M and Suba V (2022). Application of factorial design in the premixing operation of diltiazem timed-release pellets. *Ind. Pharmaceutical Sci.,* **84**(2): 390-399.

Lambros M, Tran T, Fei Q and Nicolaou M (2022). Citric acid: A multifunctional pharmaceutical excipient. *Pharmaceutics,* **14**(5): 972-989.

Lodhi VD, Jadon AS, Sen J, Jain PK, Thakur BS, Khare B and Jain A (2022). Effervescent tablets: Everything you need to know. *Asian J. Dent. Health Sci.,* **2**(4): 1-8.

Maclean N, Walsh E, Soundaranathan M, Khadra I, Mann J, Williams H and Markl D (2021). Exploring the performance-controlling tablet disintegration mechanisms for direct compression formulations. *Int. J. Pharmaceut.,* **599**: 120221.

McCrae J, Morrison E, MacIntyre I, Dear J and Webb D (2018). Long-term adverse effects of paracetamol – a review. *BJCP,* **84**(10): 2218-2230.

Pagire SK, Seaton CC and Paradkar A (2020). Improving stability of effervescent products by co-crystal formation: A novel application of crystal engineered citric acid. *Crystal Gr. Des.,* **20**(7): 4839-4844.

Patel SG and Siddaiah M (2018). Formulation and evaluation of effervescent tablets: A review. *J. Drug Del. Therapeut.,* **8**(6): 296-303.

Samiei L, Kelly K, Taylor L, Forbes B, Collins E and Rowland M (2017). The influence of electrostatic properties on the punch sticking propensity of pharmaceutical blends. *Powder Techn.,* **305**(1): 509-517.

Shi H, Mohanty R, Chakravarty S, Cabiscol R, Morgeneyer M, Zetzener H and Magnanimo V (2018). Effect of particle size and cohesion on powder yielding and flow. *KONA Powder Part. Journ.*, 2018014.

Sunand K, Sandhya V, Swapna A, Prasanth K, Vijaya A, and Geetha J (2017). Formulation design and *in vitro* evaluation of oral disintegrating tablets of selegiline. *Int. Appl. Pharmaceut. Sci.Res.,* **2**(04): 107-113.

Tannous K, Lam P, Sokhansanj S and Grace J (2013). Physical properties for flow characterization of ground biomass from douglas fir wood. *Particul.Sci. Techn.,* **31**(3): 291-300.

Taymouri S, Mostafavi A and Javanmardi M (2019). Formulation and optimization of effervescent tablet containing bismuth sub-citrate. *J. Rep. Pharmaceutical Sci.,* **8**(2): 236.

Thoke SB, Sharma YP, Rawat SS and Nangude SL (2013). Formulation development and evaluation of effervescent tablet of Alendronate sodium with vitamin D3. *J. Drug Del. Therapeut.,* **3**(5): 65-74.

USP (2021). USP 43 NF 38; Chapter 51: USP 43 - NF 38: U.S. Pharmacopoeia and National Formulary, United States Pharmacopeial Convention, Inc.

Wang Y, He F, Wang J and Hu Q (2019). Comparison of effects of sodium bicarbonate and sodium carbonate on the hydration and properties of Portland cement paste. *Materials,* **12**(7): 1-22.

Xu G, Li M and Lu P (2019). Experimental investigation on flow properties of different biomass and torrefied biomass powders. *Biom. Bioener.,* **122**(1): 63-75.

Zołek-Tryznowska Z and Kałuża A (2021). The influence of starch origin on the properties of starch films: Packaging performance. *Materials,* **14**(5): 1146.