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Original Article

DEVELOPMENT OPTIMIZATION AND EVALUATION OF EFFERVESCENT TABLETS OF CHLORPHENIRAMINE MALEATE USING BOX BEHNKEN DESIGN

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ABSTRACT

Objective: The objective of present study was to develop effervescent tablets of Chlorpheniramine maleate (CPM) for the treatment of dysphasia.

Methods: Effervescent tablets were prepared by direct compression method and were optimized using box behnken design. Amount to sodium bicarbonate (X_1), amount of tartaric acid (X_2) and amount of fumaric acid (X_3) were selected as independent variables, whereas disintegration time (Y_1), amount of carbon dioxide (Y_2) and drug release in 5 minutes (Y_3) were selected as dependent variables. All the batches were also evaluated for general post compression evaluation of tablet such as-weight variation, thickness, friability and hardness. From the results of design batches, best batch was selected and evaluated for *in vivo* pharmacokinetic study in rabbit model.

Results: The disintegration time ranged from 103.33 ± 0.24 sec to 157.00 ± 0.75 sec while amount of carbon dioxide ranged from 0.26±0.014 g to 2.03±0.056 g in all the design batches. From the results of design batches, batch B4 was selected as optimized batch due to higher amount of released carbon dioxide and faster drug release as compared to other batches. Batch B4 was showing higher AUC and C_{max} while lower t_{max} as compared to drug suspension while performing *in vivo* study of optimized batch in rabbit model.

Conclusion: The study concluded that the combination of sodium bicarbonate, tartaric acid and fumaric acid approach for development of effervescent tablet aids to achieve faster disintegration and faster drug release property for CPM.

Keywords: Effervescent tablet, Chlorpheniramine maleate, Dysphasia, Optimization, Box behnken design.

INTRODUCTION

In dysphagia, patient exhibits a problem in the throat or esophagus which causes difficulty in swallowing. In such condition, food moves back to mouth from the stomach by the muscular tube. Dysphagia can be of two types: oropharyngeal and esophageal. The problem in vacating material into the esophagus from oropharynx is known as oropharyngeal dysphagia. While, problem of passing food downward to the esophagus is known as esophageal dysphagia. Although this disease can be happening to any age of people but found commonly in elderly patient and children. In normal condition, due to throat and esophagus muscles contraction, food can easily move to the stomach. In dysphagia, muscles and nerves which help in movement of food toward stomach could not work properly which may be due to the injury in brain, problem in nervous system, esophageal spasm, inflammation in esophagus etc. Sometimes less quantity of saliva in mouth can also decrease the food movement to stomach. In such condition, only liquid or few solid dosage forms, which can be easily converted into a solution or suspension, are helpful for the treatment. Effervescent tablet is one of the best suitable dosage forms for such type of drugs [1, 2].

Effervescence is described as an expulsion of carbon dioxide gas from a fluid due to chemical reaction. This effect starts when formulation come in contact with water which works as catalyzing agent. Effervescent tablets need to be dissolved in water before administration. The tablet is promptly broken down by releasing carbon dioxide in water. Carbon dioxide produces by effervescent reaction increases the penetration of active substance into the paracellular pathway and consequently their absorption. The effervescent formulation are administered in form of solution, hence it does not come in direct contact with the gastrointestinal tract which makes such dosage forms useful for this kind of patient [3].

H_1 antagonists are used for the treatment of allergenic disorders, prurities, common cold, cough, motion sickness, vertigo etc. Parenteral H_1 antagonists are used for effective control of violent vertigo, vomiting and acute muscle dystopia. Quick relief can be achieved by administering oral effervescent formulation of H_1 antagonist in above mentioned conditions and thus helps in avoiding the invasive route for such conditions. Chlorpheniramine maleate (CPM) is a first-generation alkylamine antihistamine, used in the treatment of allergic condition such as rhinitis, urticarial and hay fever. CPM blocks certain natural histamine that body secretes during allergic reaction and acetylcholine [4, 5]. Dysphagia caused by allergic reactions and lower amount of saliva can be treated by administering CPM effervescent formulation.

Production of effervescent formulation requires higher environmental control with respect to atmospheric moisture. The ingredients, acid and carbonate or bicarbonate sources, used are very sensitive to moisture. In presence of moisture, this combination may lead to a reaction and make the product unstable [6-8]. Preliminary studies were conducted to evaluate different acid sources and the results indicated that the tartaric and fumaric acid is less hygroscopic as compared to citric acid. Development of the effervescent tablets in the present study did not require complicated technology/instruments or specific atmospheric conditions, which ultimately trim down the product cost. The objective of the present study was to prepare and evaluate an effervescent formulation of CPM which provides a quick onset of action and thereby help in treatment of allergic disorders.

MATERIALS AND METHODS

Materials

Chlorpheniramine maleate (CPM) was procured as a gift sample from Cadila Pharmaceuticals Ltd., Ahmedabad. Tartaric acid, fumaric acid, sodium bicarbonate, lactose, sodium benzoate, and sucrose were procured from Merck India Ltd., Mumbai, India. Polyvinyl pyrroledone (PVP) was purchased from Sigma Aldrich, India. All other ingredients and chemicals used in the study were of analytical grade.

Preparation of effervescent tablets

Tartaric acid, fumaric acid, sodium bicarbonate, lactose and sucrose were weight and transferred in double cone mixture (Kalweka,

Karnavati Engineering Ltd., India) for 15 min and then passes through a sieve 40#. The powder was compressed to prepare tablets (8 mm diameter) using a rotary tablet compression machine (RIMEK Mini Press II, Make: Karnavati after Engineering, Ltd. India) [9]. Developed tablets were evaluated for different evaluation parameter as per IP [10].

Experimental design

To study the effect of factors, identified during preliminary trials, on the various properties of effervescent tablets, experiments were systematically conducted by employing box behnken design. Design Expert® software (trial version 7.1.2, Stat-Ease, Inc., Minneapolis, MN) was used to graphically express the influence of each factor on the response by generating the response surface plots [11]. The amount of sodium bicarbonate (X_1), amount of tartaric acid (X_2) and amount of fumaric acid (X_3) were selected as independent variables. The dependent response variables measured were disintegration time, amount of carbon dioxide and % drug release after 5 min. The composition of design batches is shown in table 1 and levels of independent variables in coded as well as in actual form is shown in table 2. The polynomial equation created by design is as follows:

$$Y_i=b_0+b_1X_1+b_2X_2+b_3X_3+b_{12}X_1X_2+b_{23}X_2X_3+b_{13}X_1X_3 \quad (1)$$

Where Y_i is the dependent variable; b_0 is the intercept; b_1, b_2, b_3, b_{12}, b_{23}, b_{13} are the regression coefficients; and X_1, X_2 and X_3 are the independent variables. All the batches were prepared and evaluated in triplicate (n=3).

Table 1: Composition of effervescent tablets of CPM

Ingredients	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12	B13	B14	B15	B16	B17
CPM	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Sodium Bicarbonate	125	125	125	150	125	125	100	125	125	150	125	150	100	125	100	100	125
Tartaric acid	30	40	30	40	30	30	30	30	20	20	20	30	30	40	40	20	30
Fumaric acid	30	20	30	30	30	30	40	30	20	30	40	20	20	40	30	30	40
Sucrose	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
Sodium Benzoate	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Polyvinyl-pyrrolidone	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Lactose	65	65	65	30	65	65	80	65	85	50	65	50	100	45	80	100	55
Total	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300	300

All the quantities are in mg.

Table 2: Variables and their levels in box-behnken design

	Levels		
Independent variables	**Low**	**Medium**	**High**
X_1= amount of sodium bicarbonate (mg)	100	125	150
X_2= amount of tartaric acid (mg)	20	30	40
X_3= amount of fumaric acid (mg)	20	30	40
Transformed values	-1	0	1
Dependent variables			
Y_1= disintegration time (sec)			
Y_2=amount of carbone dioxide (gm)			
Y_3= Drug release after 5 min (%)			

Selection of optimized formulation was done after considering the results of dependent variables of the experimental design batches. The batch with lower disintegration time and higher carbon dioxide and drug release in 5 minutes will be considered as optimized batch. The selected dependent variables are correlated with each other because the higher amount of released carbon dioxide results in faster bursting of tablets and hence lower disintegration time and faster drug release property.

Evaluation of tablet

Post compression evaluation of tablet

Weight variation study of the tablets was performed by accurately weighing the 10 tablets individually using digital weighing balance and calculated the average weight of the tablets. Individual weights of tablets were compared with the average weight of the tablets [10]. Hardness of the tablet was studied using hardness tester (DHT-250, Cambell Electronics Machine, Thermonik) by calculating the force required to split a tablet by compression in the diametric direction. Same instrument was used to measure diameter and thickness of tablets. Friability was measured using Roche friabilator USP at 25 rpm for 4 min [12-14].

Disintegration study

The tablet disintegration time was measured as per pharmacopoeial procedure. The beaker of 250 ml was filled with 200 ml of water and one tablet was added in the beaker. The time required for a tablet to disintegrate was determined using visual observation [12-14].

Amount of carbon dioxide

The amount of carbon dioxide was measured by the method developed by G. Rajalakshmi *et al.* 10% sulfuric acid solution was prepared in distilled water. 100 ml of prepared sulfuric acid solution was taken in a beaker of 250 ml and weight of beaker was taken. One tablet was added in a beaker and tablet was observed for complete release of carbon dioxide from the tablet. Again weight of the beaker was determined and the difference in weight before and after release of carbon dioxide shows the amount of carbon dioxide generated [15, 16].

***In vitro* dissolution**

The dissolution study was executed in 500 ml of 0.01 M HCl buffer media at 37°C ± 2°C using USP apparatus II (TDT08L, Dissolution Tester (USP), Electrolab) at 50 rpm. Samples were withdrawn at time intervals of 5, 15, 30, 45, 60, 90, 120 min. The same amount of fresh dissolution medium was replaced after withdrawal of the sample. Drug content was analyzed at 264 nm by UV double beam spectrophotometer (UV 1800 Shimadzu Scientific Instrument, Japan). The cumulative percent of drug released was calculated using a calibration equation generated from the standard curve and plotted as percent cumulative drug released versus time [10].

***In vivo* study**

The *in vivo* pharmacokinetic study was carried out on the rabbit animal model (Protocol No: RPCP/IAEC/2013-2014/R-28). *In vivo* pharmacokinetic study was performed by dividing the animals in 2 groups (n=6). Animals were fasted over night and were placed in a restraining device (rabbit holder) before administration of reference (drug suspension in water) and test (optimized batch) formulations. Formulations were administered using a feeding needle. Blood samples were collected from a marginal ear vein and collected with the help of a syringe attached to a hypodermic needle. For smooth blood collection, syringe was removed from the needle and cannula was closed to prevent blood clotting. The cannula was flushed with sodium citrate solution before closing to prevent blood clotting. 1 ml of blood was withdrawn at following time interval of 30, 60, 90,1210,150 and 180 min through the cannula into 2 ml micro centrifuge tubes which contain 0.5 ml of sodium citrate solution [17].

Chromatographic conditions

Reversed phase HPLC method was used to estimate CPM in plasma samples using sensitive and validated Shimadzu LC-20AT HPLC system with SPD-20A detector (Shimadzu). The CPM was analyzed at 262 nm using UV-Visible detector. Methanol: phosphate buffer (pH 2.8) as a ratio of 60:40 was used as mobile phase and was filtered and degassed before use. The mobile phase was pumped at 1 ml/min flow rate [18].

Estimation of CPM in blood sample

Plasma aliquots of 0.5 ml was taken from rabbit plasma for analysis of CPM and transferred into a 2-mL centrifuge tube. In the same centrifuge tube, 1.5 ml of methanol was added and vortexes using a vortex mixer for 10 min at 3,000 rpm. After centrifugation, organic layer was separated and evaporated at 37 °C to get dry residue. 250 µl of mobile phase was added to dissolve the residue and from that 20µl was injected for estimation of drug content.

RESULTS AND DISCUSSION

Post compression evaluation of tablet

The results of weight variation study, shown in table 3, were not showing a significant difference in the weight of individual tablet from the average value. Average diameter and thickness of the tablets were mentioned in table 3. The diameter was found in the range of 7.44±0.014 mm to7.89±0.009 mm and the thickness was between 3.30±0.012 mm to 3.95±0.008 mm.

The hardness and friability were shown in table 3 for all the formulation. Hardness was found in a range of 1.16±0.016 kg/cm^2 to 3.94±0.008 kg/cm^2 where as friability was found in a range of 0.45±0.010 % to 0.68±0.009% which is (that is less than 1%) in the acceptable limit.

Table 3: Post compression evaluation of design batches

Batch no.	Tablet weight (mg, n=10)	Thickness (mm, n=10)	Diameter (mm, n=10)	Hardness (kg/cm^2, n=5)	Friability (%, n=5)	Drug content (%, n=5)
B1	301.00±0.82	3.87±0.017	7.77±0.09	2.86±0.012	0.68±0.009	100.42±0.289
B2	293.33±1.25	3.36±0.009	7.76±0.016	2.06±0.016	0.67±003	99.67±0.173
B3	301.00±0.82	3.34±0.017	7.87±0.019	2.57±0.029	0.66±0.019	98.75±0.346
B4	301.33±0.94	3.95±0.008	7.84±0.009	1.76±0.009	0.67±0.004	99.97±0.577
B5	298.67±0.47	3.44±0.012	7.44±0.014	2.85±0.029	0.66±0.010	100.75±0.173
B6	305.67±0.94	3.56±0.016	7.75±0.005	3.64±0.026	0.45±0.012	98.75±0.115
B7	300.67±0.94	3.32±0.012	7.75±0.009	1.95±0.022	0.45±0.316	100.33±0.231
B8	302.67±0.47	3.45±0.021	7.76±0.014	3.94±0.008	0.66±0.216	99.42±0.289
B9	297.67±0.47	3.55±0.014	7.84±0.009	2.16±0.012	0.66±0.008	100.75±0.115
B10	298.67±1.25	3.73±0.017	7.99±0.05	3.72±0.022	0.66±0.014	98.67±0.577
B11	300.33±0.47	3.59±0.012	7.77±0.00	1.30±0.012	0.66±0.017	98.42±0.321
B12	301.67±0.47	3.30±0.012	7.74±0.019	2.53±0.021	0.45±0.010	101.00±0.251
B13	302.33±1.25	3.46±0.012	7.74±0.009	2.65±0.012	0.45±0.316	99.83±0.404
B14	298.00±0.82	3.56±0.009	7.84±0.019	1.16±0.016	0.66±0.008	99.67±0.252
B15	301.67±0.47	3.42±0.019	7.89±0.005	2.16±0.012	0.67±0.004	99.42±0.451
B16	303.00±0.82	3.44±0.008	7.89±0.009	1.66±0.017	0.64±0.024	101.08±0.090
B17	295.33±0.47	3.44±0.012	7.86±0.026	2.86±0.012	0.62±0.014	100.17±0.755

Table 4: Formulation of effervescent tablets using box-behnkendesign

Batch code	X_1	X_2	X_3	Y_1 (Disintegration time) (sec, n=3)	Y_2 (amount of carbon dioxide) (g, n=3)	Y_3 (Drug release after 5 min) (%,n=3)
B1	-1	-1	0	143.66±0.603	0.27±0.072	94.3±0.398
B2	1	-1	0	150±0.998	0.33±0.062	97.06±0.875
B3	-1	1	0	103.33±0.236	0.27±0.053	95.4±0.577
B4	1	1	0	119.83±0.747	1.26±0.077	97.49±0.407
B5	-1	0	-1	148.5±0.292	0.81±0.24	95.39±0.416
B6	1	0	-1	142.66±0.490	0.34±0.068	97.19±0.458
B7	-1	0	1	145±0.399	0.26±0.014	96.06±0.529
B8	1	0	1	126.17±0.514	0.27±0.019	97.31±0.522
B9	0	-1	-1	157±0.748	0.27±0.025	92.05±0.665
B10	0	1	-1	145.17±0.564	1.1±0.021	94.82±0.769
B11	0	-1	1	146.83±0.608	0.27±0.058	95.02±0.589
B12	0	1	1	119.04±0.441	1.75±0.058	96.82±0.346
B13	0	0	0	124.33±0.625	2.03±0.056	95.231±0.513
B14	0	0	0	121.89±0.558	1.96±0.068	93.93±0.643
B15	0	0	0	123.83±0.517	1.91±0.035	94.23±0.658
B16	0	0	0	123.33±0.522	1.96±0.092	93.93±0.520
B17	0	0	0	122.17±0.847	1.83±0.040	95.92±0.501

Data analysis

Results of experimental design batches (B1 to B17) were shown in table 4. Box-Behnken design was used to optimize the amount of sodium bicarbonate, tartaric acid and fumaric acid to get the faster disintegration time and a higher amount of carbon dioxide and drug release after 5 min. The results of statistical analysis for design batches were obtained by Design Expert® software and were shown in table 4. The polynomial equation generated for each response by software was described in equation 1-3 and response surface plot for each response was shown in fig. (1-3).

Effect of disintegration time

The disintegration time ranged from 103.33±0.24 sec to 157.00±0.75 sec for all the formulations.

Disintegration time (Y_1) = $123.111-0.23*X_1-13.76*X_2-7.04*X_3+ 2.54*X_1X_2-3.25X_1X_3-3.99*X_2X_3+2.33X_1^2+3.76X_2^2+15.14X_3^2$(1)

The polynomial equation depicts that the magnitude of coefficient of X_1, X_2 and X_3 shows the negative effect which means that as the amount of all the three parameters increased, disintegration time is decreased. This might be due to faster formation of carbon dioxide because of the higher amount of these ingredients. X_2 and X_3 had shown a significant effect on the ($p<0.05$, table 5) disintegration time. The overall model was significant because the p value was<0.05. Similar results can be seen in the 3D surface plots (fig. (1)). Similar types of results were observed by Jacob *et al.* [14] while developing effervescent tablets of Glibenclamide. They observed that as the amount of disintegrating agent (sodium carbonate and acids) increased in the formulation, disintegration of tablets become fast.

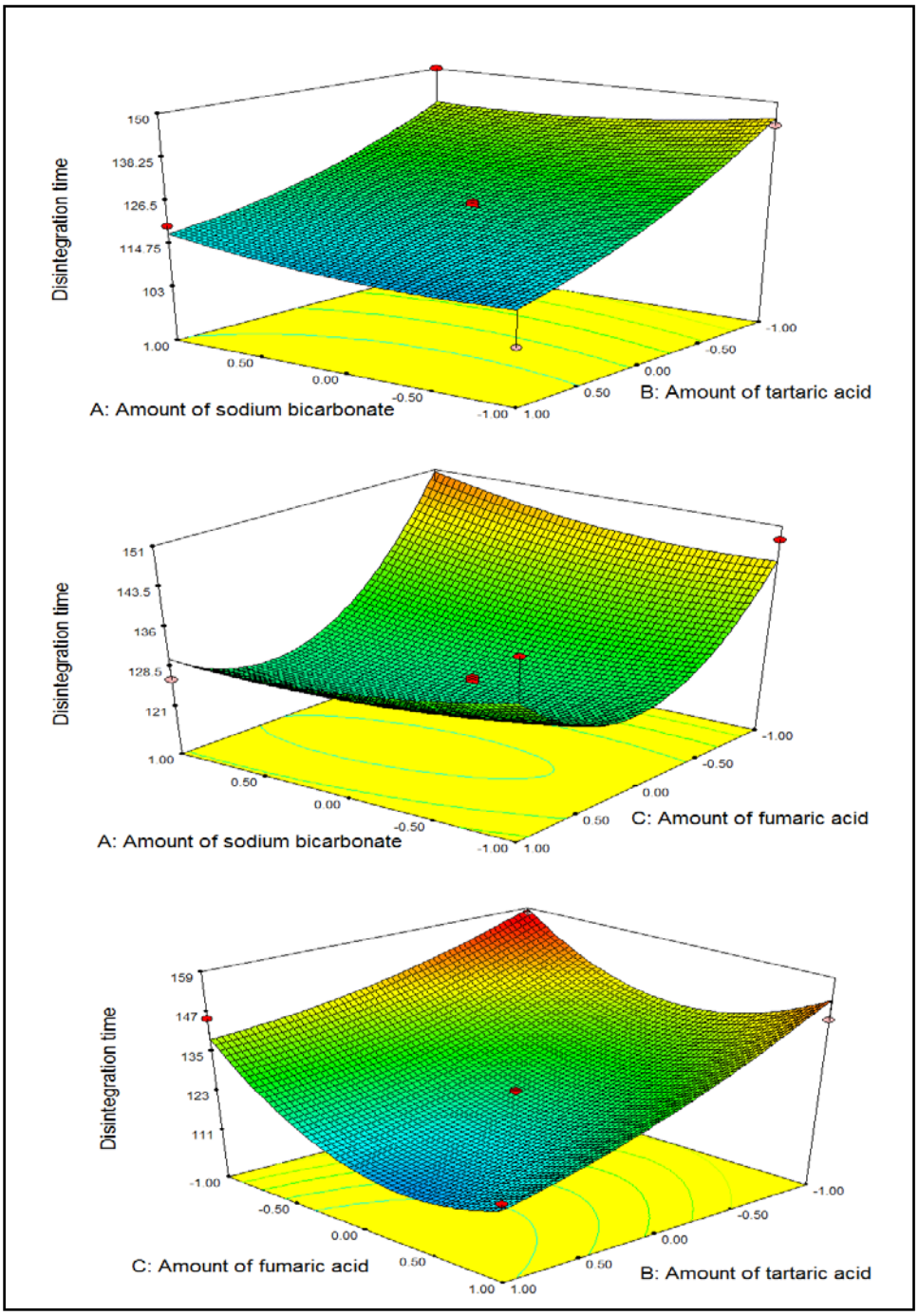

Fig. 1: 3D Surface plot for disintegration time

Table 5: Results of p value and regression coefficient

	p values of coefficients										
Responses	b_0	b_1	b_2	b_3	b_{12}	b_{13}	b_{23}	b_1^2	b_2^2	b_3^2	R^2
Disintegration time	0.0169	0.9372	0.0017	0.0402	0.5417	0.4392	0.3472	0.5645	0.3622	0.0057	0.8775
Amount of carbon dioxide	0.0045	0.5433	0.0099	0.9750	0.1975	0.4863	0.3528	0.0007	0.0180	0.0069	0.9188
Drug release in 5 min	0.0698	0.0261	0.0666	0.0796	0.7459	0.7900	0.6404	0.0126	0.6948	0.6536	0.8043

Amount of carbon dioxide

The amount of carbon dioxide ranged from 0.26 ± 0.014 gm to 2.03±0.056 gm for all the formulations B1 to B17.

Amount of CO_2 (Y_2) = $1.94+0.074*X_1+0.41*X_2+3.750E-003*X_3+0.23* X_1 X_2+0.12* X_1 X_3+0.16* X_2 X_3-0.92X_1^2-0.49X_2^2-0.60X_3^2$(2)

The polynomial equation depicts that the magnitude of coefficient of X_1, X_2 and X_3 shows positive effect and X_2 had a significant effect ($p<0.05$, table 5) on the amount of carbon dioxide. The overall model was significant because the p value was<0.05. The coefficient value of X_1, X_2 and X_3 were nearly similar. The values of interactive term for X_1, X_2 and X_3 were positive. From the 3D surface plot, as showed in fig. (2), it can also be concluded that the amount of carbon dioxide increases with increase in the amount of sodium bicarbonate, tartaric acid and fumaric acid. Similar type of results were obtained by Amela *et al.* [16] and Yanze *et al.* [19] while developing the effervescent formulation containing citric acid and sodium bicarbonate.

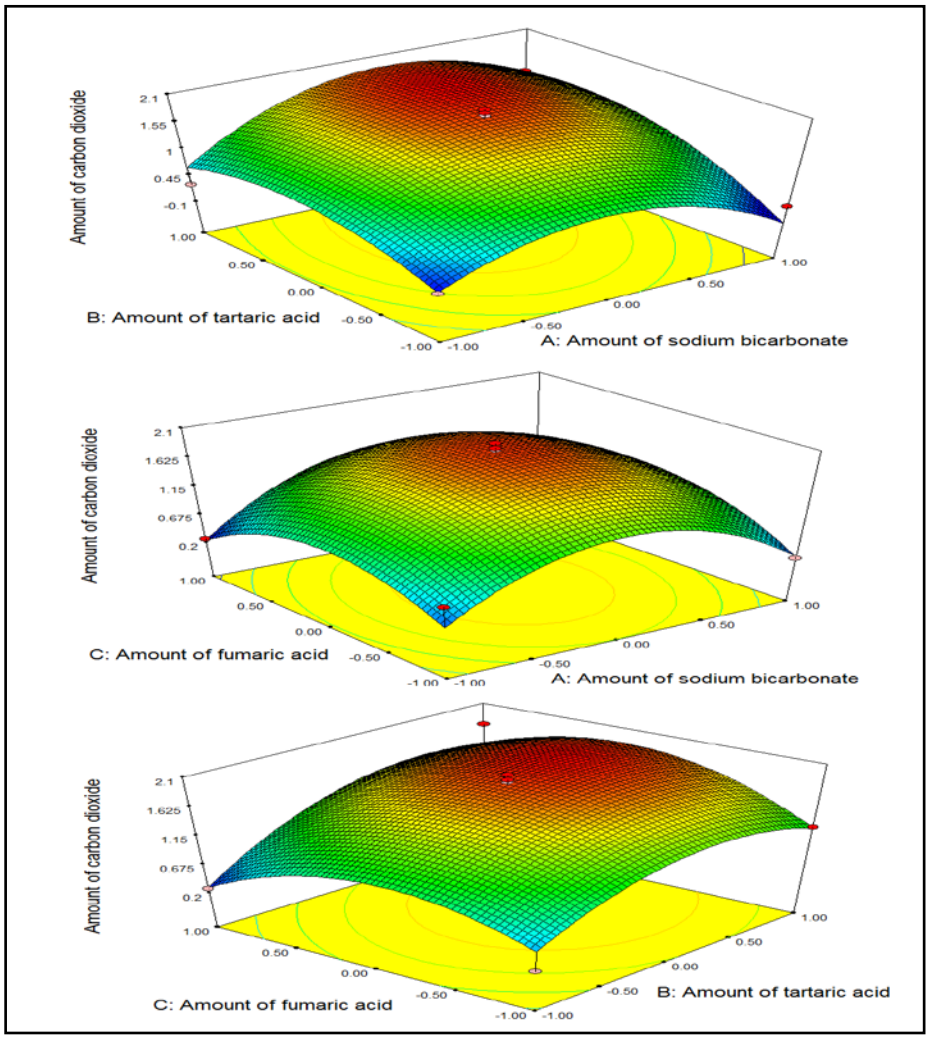

Fig. 2: 3D Surface plot for amount of carbon dioxide

Drug release after 5 min

Drug release after 5 min was obtained from92.05 ± 0.67% to 97.49 ± 0.41% for all the formulations B1 to B17.

Drug release after 5 min. (Y_3) = $94.65+0.99*X_1+0.76* X_2+0.72* X_3-0.17* X_1 X_2-0.14* X_1 X_3-0.24* X_2 X_3+1.61X_1^2-0.20X_2^2+0.23X_3^2$(3)

The polynomial equation depicts that the magnitude of coefficient of X_1, X_2 and X_3 shows positive effect and X_1 had shown a significant effect ($p<0.05$, table 5) on drug release after 5 min. 3D surface plots (fig. (3)) suggested that the higher amount of tartaric acid, fumaric acid and sodium bicarbonate gave faster drug release. All the batches were showing more than 90% drug releases after 5 minutes. Drug release profile of the design batches is shown in fig. (4). Tekade *et al.* [20] made the effervescent tablet of diclofenac sodium using the sodium bicarbonate with citric acid was showing drug release. Use of two acid sources may be the reason for faster drug release.

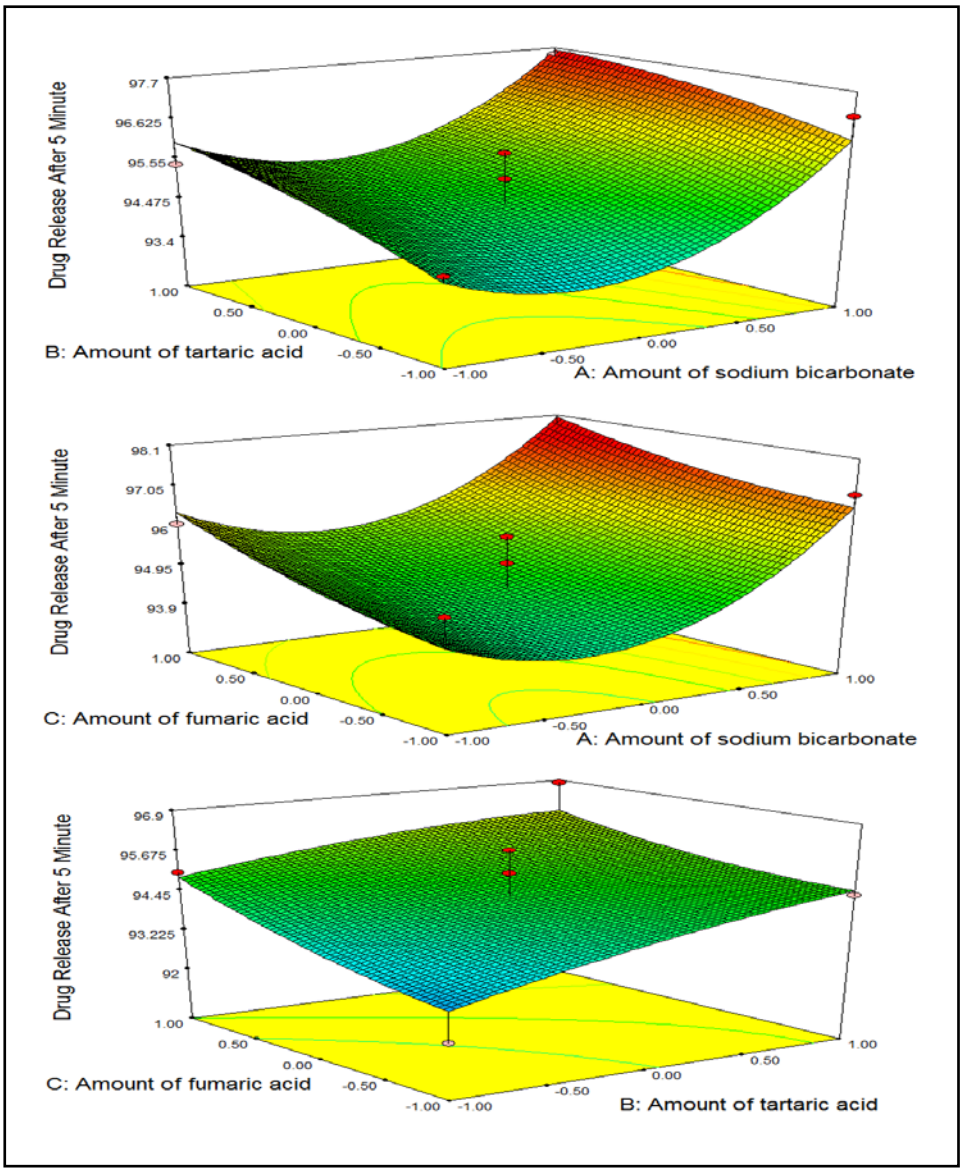

Fig. 3: 3D surface plot for drug release after 5 min

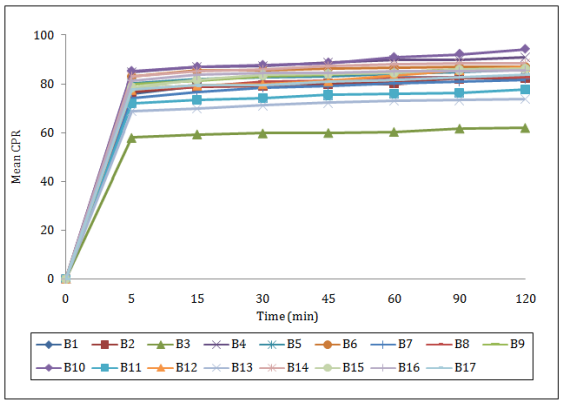

Fig. 4: Drug release of design batches

From the results of design batches, batch B4 was selected as optimized batch due to higher amount of released carbon dioxide and faster drug release as compared to other batches. Disintegration time, amount of release carbon dioxide and drug release in 5 minutes for batch B4 were 119.83 ± 0.78 sec, 1.26 ± 0.58 and 97.49 ± 0.41% respectively. This batch was further subjected to *in vivo* study using a rabbit model.

***In vivo* study**

Standard solution of CPM was prepared in the mobile phase of methanol: phosphate buffer (pH6.8) with a ratio of 60:40. Different dilutions were made and 20 µl was injected to HPLC system. Same process was done in triplicate to measure the reproducibility of results. The results showed good correlation between the concentration of CPM and peak area, and linear relationships in plasma concentration ranging from 500 ng/ml. to 5500 ng/ml. The method used for analysis was reproducible with good precision which can be concluded from its percentage accuracy for intra-day and inter-day studied batches and was complied with the limit of 85-115%.

The maximum plasma concentration (C_{max}), time to reach the maximum plasma concentration (t_{max}), area under the drug plasma concentration-time curve up to 2 h post-administration (AUC 0-2 h) and the elimination half-life ($t_{1/2}$) was calculating using non

compartmental analysis and are shown in table 6. From the fig.(5), t_{max} was higher in case of effervescent tablet solution of batch B4 compared to drug suspension.

Table 6: Pharmacokinetics parameters of reference and optimized batch formulations

Parameter	Reference	Optimized batch (B4)
AUC (0-180 min)	71.4	73.86
t_{max}(min)	90	60
C_{max}(ng/ml)	2.74	2.76

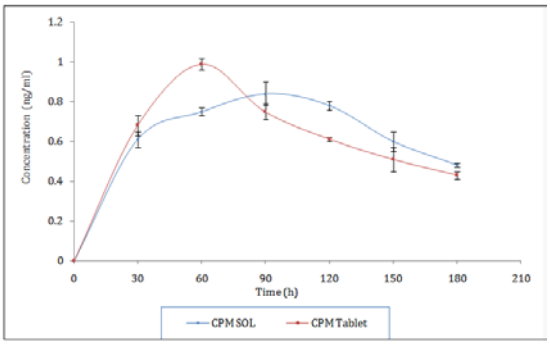

Fig. 5: Drug release in rabbit plasma

CONCLUSION

The study concluded that the combination of sodium bicarbonate, tartaric acid and fumaric acid approach for development of effervescent tablet aids to achieve faster disintegration and faster drug release property for CPM. The Box-Behnken design was employed for the optimization and studies the effect of process parameters and their interaction on the effervescent formulation. Optimized batch B4 was showing higher amount of released carbon dioxide and faster drug release as compared to other batches. Batch B4 was also showing a higher AUC and C_{max} while lower t_{max} as compared to drug suspension while performing *in vivo* study of optimized batch in rabbit model. Thus, it could be concluded that the combination of acids and sodium bicarbonate helps to develop effervescent tablets. Use of experimental design might be helpful to develop effervescent formulation with desired characteristics like faster disintegration and drug release with minimum efforts in the shortest time.

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CONFLICT OF INTERESTS

Declared None

REFERENCES

1. Hassan HE, Aboloyoun AI. The value of bedside tests in dysphagia evaluation. Egyptian J Ear Nose Throat Allied Sci 2014;15(3):197–203.
2. Huang KL, Liu TY, Huang YC, Leong CP, Lin W C, Pong YP. Functional outcome in acute stroke patients with oropharyngeal dysphagia after swallowing therapy. J Stroke Cerebrovasc Dis 2014;23(10):2547-53.
3. Bodmeier RA, Swarbrick J, BoylanJ C. Encyclopedia of Pharmaceutical Technology: 3rd ed. Informa Healthcare 2006;3. p. 1454-65.
4. Tripathi KD. Essential of Medical Pharmacology, Section 3, Autacoids and Related Drugs, Histamine and Antihistamine. 6th ed. Jaypee Brothers Medical Publisher (P) Ltd, New Delhi; 2013. p. 151-61.
5. www.webmd.com/drugs/2/drug-4156/chlorpheniramine-oral/details#uses. [Last accessed on 12 Mar 2015].
6. Mohapatra A, Parikh RK, Gohel MC. Formulation, development and evaluation of patient friendly dosage forms of metfoming. Part III: Soluble effervescent tablets. Asian J Pharm 2008;2(3):177-81.
7. Rowe RC, Sheskey PJ, Quinn ME. Handbook of pharmaceutical excipients, GE Amidon (Citric Acid), PJ Weller (Fumaric Acid), CG Cable (Sodium Bicarbonate). 6th ed. Pharmaceutical Press: American Pharmacist Association; 2012. p. 181, 276, 629.
8. Mohrle RLH, Lachman L, Schwartz, J. Pharmaceutical dosage forms: Tablets. First Indian Reprint ed. New York: Marcel Dekker Inc; 2005. p. 285-92.
9. Khan A, Iqbal Z, Rehman Z, Nasir F. Application of Se De Mexpert system in formulation development of effervescent tablets by direct compression. Saudi Pharm J 2014;22(5):433–44.
10. Indian Pharmacopoeia. Ghaziabad: Indian Pharmacopoeial Commission, Govt. of India-Ministry of Health and Family Welfare; volume II; 2007. p. 43.
11. Solanki AB, Parikh JR, Parikh RH. Formulation and optimization of piroxicamproniosomes by 3-Factor, 3-Level box-behnken design. AAPS Pharm Sci Tech 2007;8(4):E1-E7.
12. Swamy PV, Divate SP, Shirsand SB, Rajendra P. Preparation and evaluation of orodispersible tablets of pheniramine maleate by effervescent method. Indian J Pharm Sci 2009;71(2):151-4.
13. Nagendrakumar D, Raju SA, Shirsand SB, Para MS, Rampure MV. Fast dissolving tablets of fexofenadine HCl by effervescent method. Indian J Pharm Sci 2009;71(2):116-9.
14. Jacob S, Shirwaikar A, Nair A. Preparation and evaluation of fast-disintegrating effervescent tablets of glibenclamide. Drug Dev Ind Pharm 2009;35(3):321-8.
15. Rajalakshmi G, Vamsi CH, Balachandar R, Damodharan N. Formulation and evaluation of diclofenac potassium effervescent tablets. Int J Pharm Biomed Res 2011;2(4):237-43.
16. Amela J, Salazar R, Cemeli J. Methods for the determination of the carbon dioxide evolved from effervescent systems. Drug Dev Ind Pharm 1993;19(9):1019-36.
17. Gauniya A, Das S, Mallick S, Basu SP. Comparative bioavailability studies of citric acid and malonic acid based aspirin effervescent tablets. J Pharm Bioallied Sci 2010;2(2):118-20.
18. Senyuva H, Ozden T. Simultaneous high-performance liquid chromatographic determination of paracetamol, phenylephrine HCl, and chlorpheniramine maleate in pharmaceutical dosage forms. J Chromatogr Sci 2002;40(2):97-100.
19. Tekade BW, Jadhao UT, Thakre VM, Bhortake LR. Formulation and evaluation of diclofenac sodium effervescent tablet. Innovations Pharm Pharmacother 2014;2(2):350-8.
20. Yanze FM, Duru C, Jacob M. A process to produce effervescent tablets: fluidized bed dryer melt granulation. Drug Dev Ind Pharm 2000;26(11):1167-76.