WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 21, 723-736. Research Article ISSN 2277–7105

DEVELOPMENT, CHARACTERIZATION AND FUNCTIONALITY EVALUATION OF EFFERVESCENT GRANULES IN ASCORBIC ACID EFFERVESCENT TABLET FORMULATION BY DIRECT COMPRESSION

Amit Raj Sinha[1*], Dr. Viraj Kulthe[2] and Rauf Pathan[2]

[1]SIGACHI® Industries Limited, 2nd Floor, Kalayan's Tulsiram Chambers, Madinaguda, Hyderabad, Telangana, India.

[2]SIGACHI® Industries Limited, Dahej SEZ, Bharuch, Gujarat, India.

Article Received on
06 September 2024,

Revised on 27 Sept. 2024,
Accepted on 17 October 2024

DOI: 10.20959/wjpr202421-34240

***Corresponding Author**
Amit Raj Sinha
Sigachi® Industries Limited, 2nd Floor, Kalayan's Tulsiram Chambers, Madinaguda, Hyderabad, Telangana, India.

ABSTRACT

Unit dosage forms, like effervescent tablets are portable and easier to swallow than conventional tablet and liquid formulations. This increases their acceptability and compliance by the patients. Also, they are preferred alternatives to liquid dosage forms for substances exhibiting insufficient stability in aqueous vehicle during storage. A few active substances, like ascorbic acid (vitamin C) are relatively stable in air in their powder form. However, it is unstable in solution undergoing oxidation, in presence of air and light. Thus, formulating moisture-sensitive ingredients, like ascorbic acid into effervescent tablets by wet granulation technique becomes difficult. The present study addresses this challenge by modifying the method of manufacturing effervescent tablets. Readily compressible effervescent granules were obtained by co-processing mannitol, sodium bicarbonate, citric acid and polyvinylpyrrolidone. Then ascorbic acid was formulated into tablet dosage forms by direct compression method containing such co- processed granules and evaluated. This study demonstrated enhanced processability, powder micromeritics, physical stability and performance of the formulation containing ascorbic acid. Thus, the present study highlighted the significance of using co-processed effervescent granules in formulating moisture-sensitive active ingredients into directly compressible tables.

KEYWORDS: Effervescent granules, effervescent tablet, moisture sensitive, ascorbic acid, direct compression, co-processed excipient.

INTRODUCTION

Oral drug delivery has been known for decades as the most popular route of drug administration among all other routes. One of the reasons that the oral route achieved such acceptance is its ease of administration.[1] Effervescent tablets gained preference over liquid dosage forms for the reasons being unit dosage forms, portable in nature, palatable, ease of preparation and storage stability.[2] Such tablets are designed to disperse in contact with water often causing the tablets to dissolve into a solution.[3] Further, effervescent tablets contain acidic and basic ingredients, which impart effervescent functionality to the tablet formulation. However, processing such ingredients by aqueous wet granulation tablet manufacturing technique may be challenging. This is because they react instantaneously and disperse by addition of aqueous binder systems. Also, moisture sensitive active ingredients like vitamins, minerals, herbal extracts and probiotics are highly susceptible to degradation or modification when exposed to moisture. Hence, preserving their integrity throughout manufacturing ensures potency and efficacy of the final product is a task.

Direct compression is the preferred manufacturing method for obtaining such effervescent tablets for several reasons. It preserves the integrity of ingredients; it is cost-effective, and it speeds up production.[4] However, formulating active ingredients with cohesive nature, poor flow and compressibility properties in final blend would be most intriguing challenge. So, co-processing excipients like sodium bicarbonate or magnesium bicarbonate, with citric acid or tartaric acid, which are known for imparting effervescence functionality to these granules seems to be a lucrative approach. And use of such dense, free- flowing, directly compressible granules for formulating tablets containing hygroscopic or moisture-sensitive actives makes this approach commercially viable. Liberation of carbon dioxide during reconstitution will also enhance dissolution of the active ingredient and mask unacceptable taste of the actives.[5]

Market review suggested us that no manufacturer had commercialized ascorbic acid effervescent tablet using direct compression method. The obvious reasons would be crystalline and hygroscopic nature of citric acid made its mixing with other tablet ingredients difficult. This might be resulting into segregation or separation of actives. Additionally, tablet sticking and picking defects during tablet compression process also made its execution difficult.[6] Specifically, ascorbic acid possesses poor flow and compactability properties. It is

also unstable in aqueous solution and even aqueous binder solution added during granulation process can degrade it. To address all these predicaments, we proposed an approach of formulating effervescent granules by wet granulation method.[7] These granules contained sodium bicarbonate as an alkalizing agent, citric acid used as an acidifying agent, mannitol used as a sweetener and filler; and povidone used as a granulating agent.[8] These granules were characterized by Fourier transform infrared spectroscopy and physical properties like bulk density, particle size distribution, flow rate, compressibility index, Hausner's ratio and angle of repose were studied. And the tablet formulations were studied for hardness, weight variations, friability, effervescence time and effervescent solution pH.[9] In this article, we have ascertained an impact of co-processing excipients to obtain effervescent granules, formulating effervescent tablet using these granules by direct compression method and evaluate their performance and stability. The study demonstrated that effervescent granules helped to increase flowability and compressibility of challenging actives and it overcome tablet defects during tablet manufacturing by direct compression method.

MATERIAL AND METHODS

Effervescent granules were manufactured at SIGACHI® industries Limited, Dahej, Gujarat (India). Mannitol was purchased from Labort Fine Chem Private Limited Gujarat (India). Sodium bicarbonate and citric acid were procured from Sujata Nutri-pharma Private Limited Gujarat (India). Ascorbic acid was obtained from Xinjiang Oiyuan Pharmaceutical Co. Limited (China). Povidone (PVP K-30) was purchased from Ashland cellulose (India). Other chemicals of analytical reagent grade used in this study were sourced locally.

Co-processing of directly compressible effervescent granules by wet granulation

The required ingredients listed in Table 1 were weighed accurately by using an analytical weighing balance (Make: Mettler Toledo Japan, Model: ME303/A04). They were co-sifted through 30 mesh stainless steel sieve and mixed in a high shear granulator (Make: Gem Pharma Machineries India, Model: 5KGS) with impeller rotations for 10 - 12 minutes at 50 - 55 rotations per minute (rpm). The binder solution was prepared by dissolving povidone (PVP K-30) in isopropyl alcohol using overhead stirrer. Then this binder solution was gradually added to the blend in high shear granulator with impeller rotation for 30 - 40 minutes at 75 - 80 rpm and chopper speed for 30 - 40 minutes at about 1200 - 1600 rpm. Then this damp mass was passed through 30 mesh stainless steel sieve. Then these damp granules were dried using hot air oven (Make: Janki India, Model: JI-65) on trays till loss on

drying (LoD) obtained was not more than 5% at 105 °C for 5 minutes tested using halogen moisture analyzer (Make: Scale-TEC India, Model: AGS-120/IR). Final granule sizing of these dried granules was done by passing them through 30 mesh stainless steel sieve.

Table 1: Composition of effervescent granules.

Ingredients	Percentage
Mannitol	55.0% - 65.0%
Sodium bicarbonate	20.0% - 30.0%
Citric acid	12.0% - 20.0%
PVP K-30	1.0% - 3.0%
Isopropyl alcohol	Quantity sufficient

Formulation of Ascorbic acid tablets using effervescent granules

Accurately weighed quantities of ascorbic acid (previously sifted through 40 mesh stainless steel sieve), effervescent granules and other tablet excipients (previously sifted through 40 mesh stainless steel sieve) were transferred into a blender of appropriate capacity (Make: Reva Pharma Machinery India, Model: TRMIX-20). These materials were mixed for 8 - 10 minutes at 25 rpm. To this blend, an accurately weighed quantity of lubricant (previously sifted through 60 mesh stainless steel sieve) was added and mixed for not more than 3 minutes at 25 rpm to obtain a final blend. The final blend was characterized by angle of repose, bulk density, Hausner's ratio and compressibility index parameters. Then this blend was compressed into tablets by using 12 station tablet press (Make: Eliza Press India, Model: EP-200) fitted with "D" tooling sets. Different compositions of effervescent tablets were formulated as shown in Table 2. To evaluate functionality of effervescent granules, initially four different formulation approaches were designed (entitled F1, F2, F3 and F4) given in Table 3. As a standard requirement, relative humidity in the processing area was maintained below 45% RH and temperature was maintained below 25°C to ensure unchanged product quality.

Table 2: Various formulations of ascorbic acid effervescent tablet.

Ingredients	mg/tablet			
	F-1	F-2	F-3	F-4
Ascorbic Acid (Vitamin C)	500.0	500.0	-	500.0
Effervescent Granules	-	-	-	1900.00
Effervescent Granules (Physical Blend)	-	1900.00	-	
Mannitol	1140.00	-	1140.00	-
Sodium Bicarbonate	513.00	-	513.00	-
Citric Acid	247.00	-	247.00	-
Vanilla Flavor	25.00	25.00	25.00	25.00

Macrogol 6000	75.00	75.00	75.00	75.00
Average Tablet Weight (mg)	**2500.0**	**2500.0**	**2000.0**	**2500.0**

Excipients compatibility studies

Molecular interactions in effervescent granules were studied using Fourier transform infrared spectroscopy (FTIR) (Make: Shimadzu Japan, Model: IR Spirit-S) and the spectrum was recorded in the wavelength region from 4000 to 400 cm^{-1} by using diffuse reflectance system (DRS) method. The procedure consisted of mixing a sample with potassium bromide and placing it into sample disc.[10]

Evaluation of physical properties of effervescent granules

Untapped bulk density

Untapped bulk density analyzed using volumeter by the method mentioned in United States Pharmacopoeia: General Chapter on bulk density <616>.[11]

Tapped bulk density

Tapped bulk density is determined by placing a graduated cylinder by the method mentioned in United States Pharmacopoeia: General Chapter on tapped density <616>.[12]

Hausner's ratio

It is an indirect index of measuring granules flow by the method mentioned in United States Pharmacopoeia: General Chapter on powder flow <1174>. Lower Hausner's ratio (<1.25) indicates good flow property of granules.[13]

Compressibility index (Carr's index)

It is an indirect index of measuring granules flow by the method mentioned in United States Pharmacopoeia: General Chapter on powder flow <1174>.[13] Lower Carr's index (between 15 and 20%) indicates fair compressibility property of the granules.

Angle of repose

It was determined by the method mentioned in United States Pharmacopoeia: General Chapter on powder flow <1174>.[13] Table 3 below mentions the flow of the granules based on angle of repose measurements.

Table 3: Angle of repose as an indication of granules flow properties.

Angle of Repose (º)	Type of Flow
< 20	Excellent
20-30	Good
30-34	Passable
> 40	Very Poor

Flow rate

The flow rate of granules was determined using Flodex flowability tester (Make: Hanson, United States of America). It was performed by pouring accurately weighed granules in funnel with an orifice of 10 mm diameter. The time required for the complete granule mass to emerge out of the orifice was recorded using a calibrated stopwatch. The flow rate was calculated from the following equation.[14]

Weight variation

Weight variation was determined to know if different batches of tablets have uniformity. It was determined by the method mentioned in United States Pharmacopoeia: General Chapter on uniformity of dosage units <905>.[15] Weight variation specification as per IP/BP and USP is shown in Table 4.

Table 4: Weight variation specification.

IP/BP	Limit	USP
80 mg or less	± 10.0%	130 mg or less
More than 80 mg or Less than 250 mg	± 7.5%	130 mg to 324 mg
250 mg or more	± 5.0%	More than 324 mg

Measurement of effervescent time

A single tablet is placed in a beaker containing 200 mL of DM water at 20°C ± 1°C temperature. When a clear solution without particles is obtained the effervescence time has finished. Note down the time of effervescence. The mean of three measurements of each formulation is to be reported.[16]

Measurement of solution pH

pH of solution was determined with one tablet in 200 mL of DM water at 20°C ± 1°C by using pH meter (Make: Toshniwal India, Model: $CL54^{+}$), immediately after completing the effervescent (n= 3).

Thickness

Thickness of tablets was important for uniformity of tablet size. Thickness was measured by using digital tablet thickness tester machine (Make: Labindia India, Model: TH1050M).

Tablet strength

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by digital tablet hardness tester. The hardness was measured in terms of [Kp(kgf)]. Hardness or tablet crushing strength is the force required to break a tablet in a diametric compression. The force is measured in [Kp(kgf)] and tablet hardness of about 5.0 -10.0 [Kp(kgf)] is considered to be satisfactory for uncoated tablets.[17]

Friability

15 tablets were weighed accurately. These tablets were subjected to combined effect of attrition and impact by using a friabilator (Make: Labindia India, Model: FT1020) 100 and 200 revolutions at 25 rpm. The tablets were reweighed after the test. The percentage friability was calculated by below mentioned formula, which should not be more than (NMT) 1.0% as mentioned in the USP.

***In-vitro* dissolution profile**

Dissolution profile of ascorbic acid in effervescent tablet was performed using dissolution test apparatus (Make: Labindia India, Model: DS8000), by using USP 44 compendial method (n=3), apparatus No. II (paddle), speed 50 RPM for 60 minutes in 900 mL of de-mineralized water at 37 ± 0.5°C medium temperature. Each of randomly selected 6 tablets were introduced in each dissolution vessel. Sample aliquots of 5 mL were withdrawn from each dissolution vessel at different time intervals such as 5, 15, 30, 45 and 60 minutes. After withdrawal, samples were filtered through whatman filter paper (No. 42). 1 mL filtrate from the beaker was taken and transferred into 10 mL of volumetric flask and diluted up to 10 mL with dissolution medium. The same procedure was repeated for all remaining 5 tablets. Standard and sample absorbances were recorded using UV visible spectrophotometer (Make: Shimadzu Japan, Model: UV-1900) at λ= 258 nm wavelength. Ascorbic acid drug released from the tablet formulations was calculated using below mentioned formula.[18]

Amount of drug released (mg) = Concentration of released drug × Dilution factor × Volume of dissolution medium / 1000

Drug released (%) = Amount of drug released (mg) / label claim (mg) x 100

RESULTS AND DISCUSSION

Characterization of effervescent granules

Drug excipients compatibility studies

FT-IR spectra of the formulation and ascorbic acid were found to be superimposable. There were no additional peaks observed in the functional group and fingerprint regions in the spectra of formulations. This indicated that there was no alteration in the molecular structure and functional groups in the effervescent granules. This study proposed that ascorbic acid was chemically intact in presence of mannitol, sodium bicarbonate and citric acid.

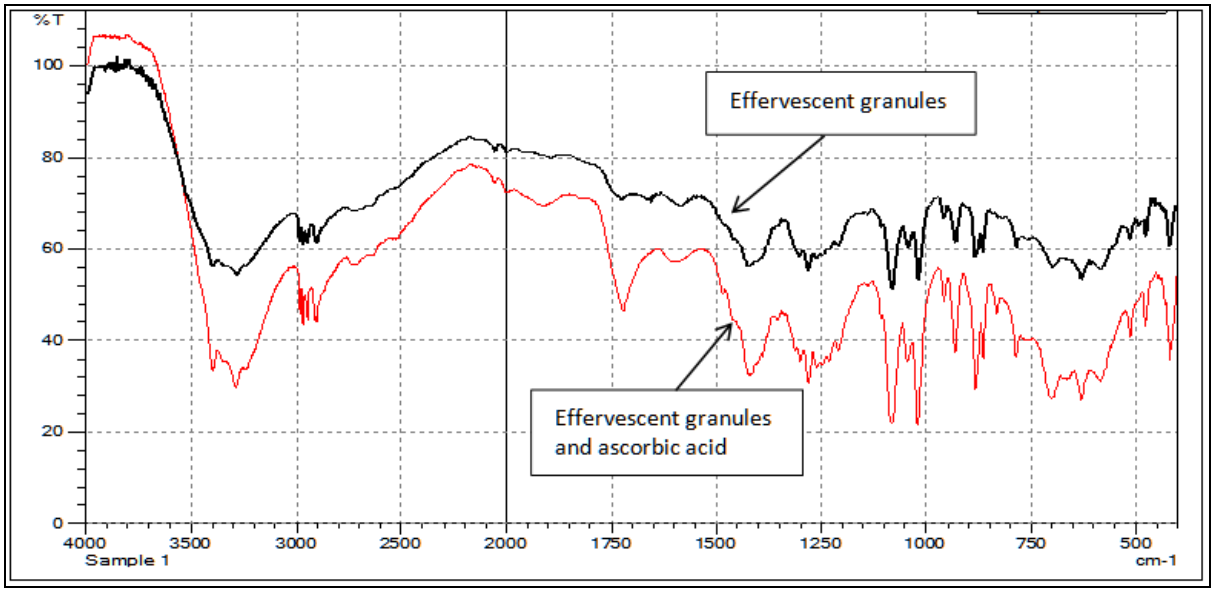

Fig. 1: FTIR spectrum comparison of effervescent granules and mixture of effervescent granules and ascorbic acid.

Evaluation of pre-compression and post compression parameters

In an effort to obtain ascorbic acid formulations with improved density, flow and compressibility properties compared with ascorbic acid and to discriminate one from the other, different formulation approaches were designed (i.e Formulation F1- F4) as mentioned in Table 3. These involved blends obtained by physical mixing individual excipients (with and without ascorbic acid) and mixing ascorbic acid with effervescent granules. The results for the pre-compression parameters of ascorbic acid and various formulation (F1– F4) are listed in Table 5.

Table 5: Result of pre-compression parameters of ascorbic acid and formulation F1-F4.

Material	Angle of Repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Flow Rate (g/second)	Carr's Index (%)	Hausner's ratio
Ascorbic Acid	45	0.68	0.89	1.8	23.60	1.31
F1	41	0.64	0.83	2.9	22.89	1.30
F2	43	0.58	0.78	2.1	25.64	1.34
F3	48	0.50	0.69	1.4	27.53	1.38
F4	32	0.59	0.67	4.1	11.71	1.13

Angle of repose values for ascorbic acid and formulation F1, F2 and F3 were found to be higher than 25°, which indicated poor flow property. This could be attributed to hygroscopic nature of citric acid. This has resulted into poor flow properties of the blend, improper die filling leading to tablet weight and content variations also. Whereas F-4 demonstrated excellent flow property, with less angle of repose values as compared to the other formulations as shown in Figure 2.

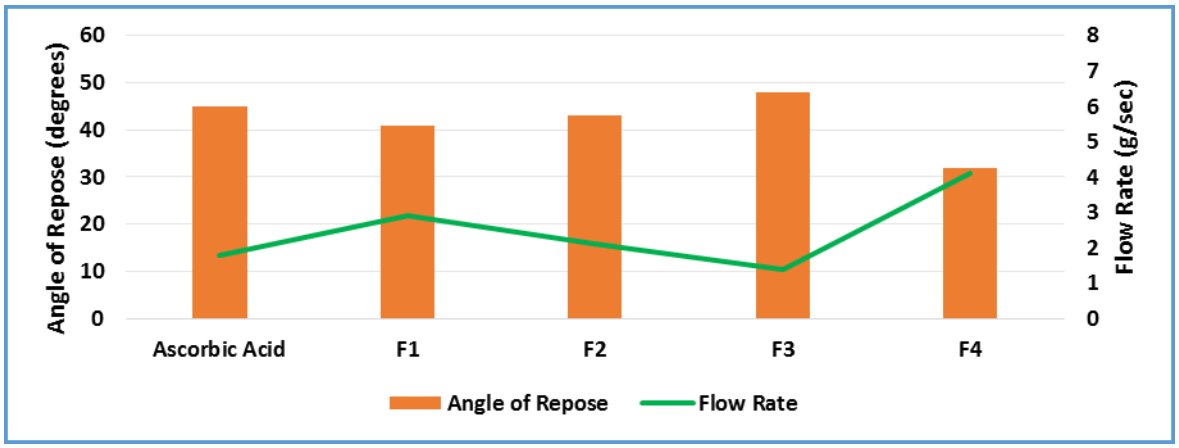

Fig. 2: Comparison of flow properties of ascorbic acid and its formulations, F1 - F4.

Hausner's ratio is influenced by variables such as particle size, shape and blend cohesiveness, since they essentially reflect the impact of tapping on the particles packing.[19] F4 showed much better Carr's index values (between 10 and 13%) compared with that of F1, F2 and F3 (more than 22%) depicted in Figure 3. This represent processing superiority of F4 over other formulations.

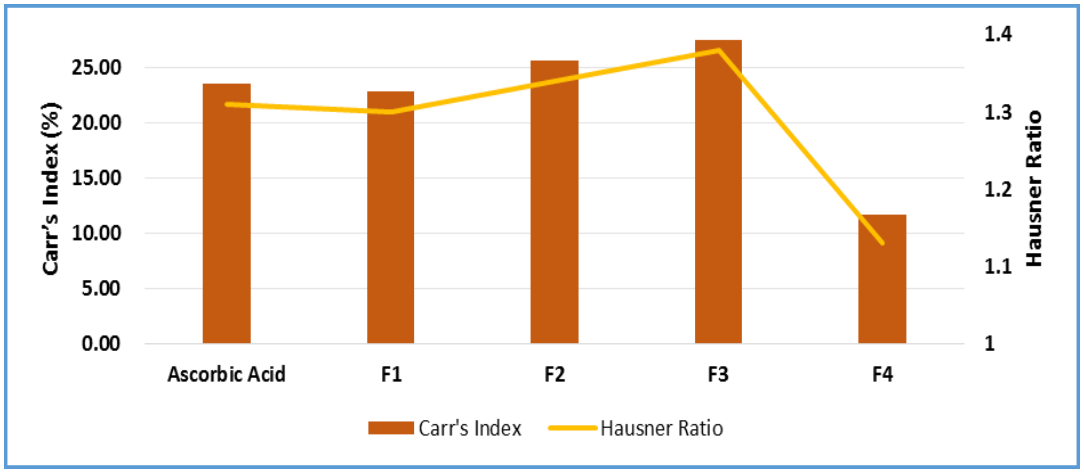

Fig. 3: Comparison of compressibility profile of various formulations, F1 - F4.

In tablet formulations obtained using F1 and F2, sticking problem was observed during tablet compression on both lower and upper punch faces. To deal with this problem, it was necessary to know whether the problem lies with ascorbic acid or any of the excipients in the formulation. Therefore, placebo tablets (F3) were compressed without adding ascorbic acid. However, a sticking problem was observed in this formulation also. Further studies showed that mainly citric acid had a tendency to adhere to the punch surfaces due to its hygroscopic nature. To overcome this problem, an approach of preparing directly compressible effervescent tablets of ascorbic acid containing ready- to- use effervescent granules was developed. This formulation (F4) demonstrated good compressibility and flow property of the final blend. The compressed tablets did not show any tablet defects such as sticking, weight or content variations. These tablets were characterized for effervescent time, effervescent solution pH, friability, hardness, thickness, diameter and *in-vitro* drug release also. Properties of effervescent tablet are summarized in Table 6.

Evaluation of ascorbic acid effervescent tablet

Tablet formulations containing F4 showed better appearance than the tablets containing F1, F2 and F3 formulations. All the tablets passed the weight variation test, as the percent weight variation was within pharmacopoeial limits of ±5% of the weight. This ensured content uniformity of tablets containing hygroscopic actives, like ascorbic acid in presence of dense, free flowing and directly compressible effervescent granules.

The average tablet weight was found to be almost similar to marketed tablet as mentioned in Table 6. Effervescent tablet containing F4 had thickness of about 6.00 mm comparable to that of marketed tablet (about 5.70 mm).

Table 6: Post compression parameters of ascorbic acid effervescent tablet.

Parameters	Observations	
	Tablet containing F4	Marketed Tablet
Tablet weight (mg)	2501	2468
Tablet hardness [Kp(kgf)]	9.83	7.04
Thickness (mm)	5.90 ± 0.10	5.68 ± 0.10
Friability (%)	0.260	0.484
Effervescent time (second)	62.0 ± 3.00	74.0 ± 5.00
Effervescent solution pH	5.58 ± 0.05	5.50 ± 0.05
Drug released (%) after 60 minutes	100.5	98.92

Effervescent tablets, because of their inherent brittle nature and being bigger in dimension, are more friable.[20] However, the resistance to breakage and lesser friability of the tablets containing F4 was an indication of improved tablet strength (Table 6). Thus, effervescent tablets of ascorbic acid of better quality could be formulated using ready- to- use effervescent granules than the conventional means of obtaining effervescent tablets.

Figure 4 depicted linearity of the spectrophotometric method used to estimate content of ascorbic acid and drug released from the tablet formulations.

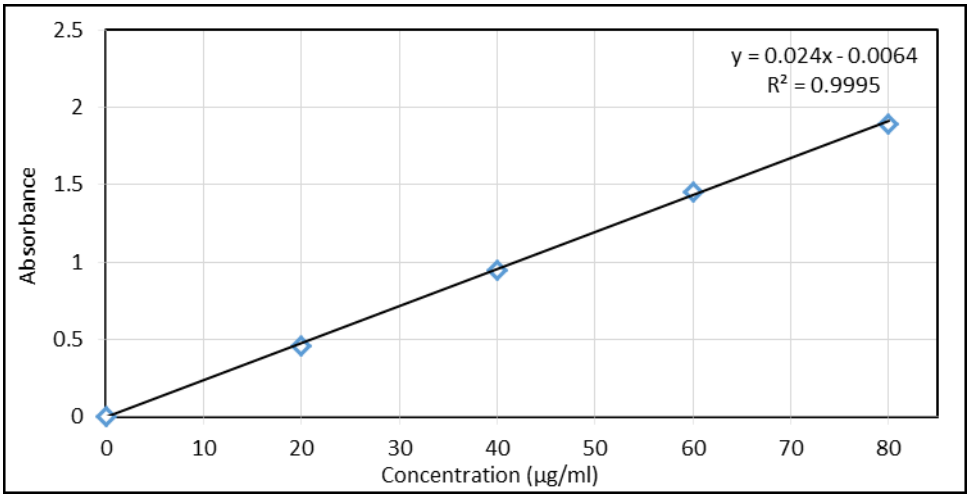

Fig. 4: Standard calibration curve of ascorbic acid.

The percent amount of ascorbic acid released from the effervescent tablet formulations in water after 5 minutes are presented in Table 6. The amount of drug released from formulated tablet and marketed tablet was found to be comparable. Such improvement in dissolution of ascorbic acid in effervescent tablet occurred due to rapid disintegration and bursting effect exerted by effervescence reaction.[21]

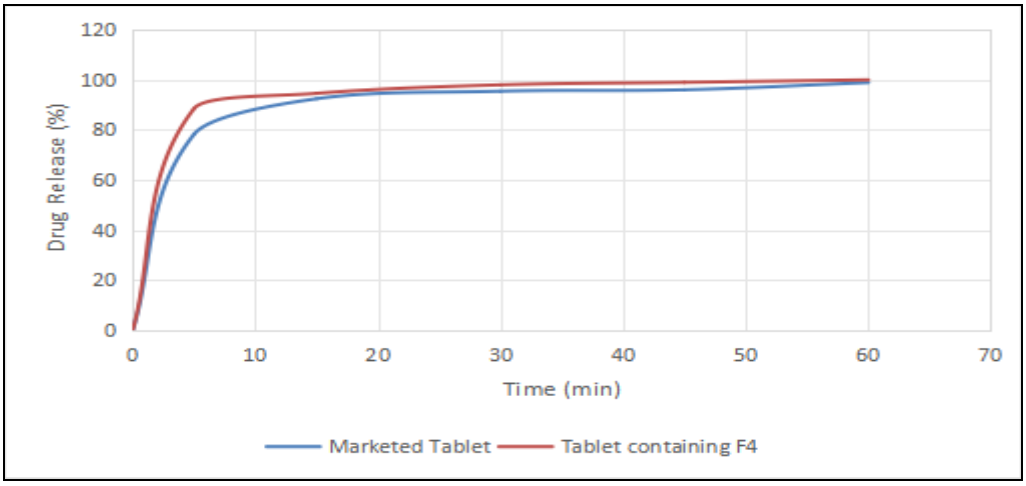

Fig. 5: Drug released profile of ascorbic acid effervescent tablet.

(Dissolution medium: De-mineralized water & Apparatus USP Type II)

Effervescence time of ascorbic acid effervescent tablet is shown in Table 6. The effervescent time of the tablets containing F4 formulation was found to be close to 1 minute, which was slightly better than that of marketed tablet. Effervescent solution pH measured after complete disintegration of effervescent tablet into water and effervescence has ceased was found to be comparable to that of marketed tablet (Table 6). This suggested that the approach of formulating ascorbic acid using ready- to- use effervescent granules had produced the tablets of comparable performance also.

CONCLUSION

Effervescent tablets are a lucrative alternative to regular oral tablets as they are easy to administer. Patient acceptance and compliance of former tablet formulations is more in elderly patients with swallowing problems, as they need to be taken after dissolving in water and no need to be swallowed. These tablets are conventionally manufactured by wet granulation method considering higher friability and poor compaction of the materials. However, this leads to processing challenges for moisture sensitive actives and poses a stability concern also. In this study, we demonstrated that effervescent granules obtained by co-processing the necessary ingredients had outstanding physico-chemical properties like flow properties, higher bulk density and better compressibility. Such optimized formulation of effervescent granules was further used to formulate moisture sensitive actives, like ascorbic acid into effervescent tablets by direct compression technique. It had helped to increase ascorbic acid blend flowability, compressibility and minimize tablet weight variation, tablet defects when formulated by direct compression method. Such granules also

provided higher tablet hardness with less effervescent solution time, less friability, maintain solution pH and improved drug release profiles.

CONFLICT OF INTEREST

The authors state and confirm no conflict of interest. No direct funding was received for this study.

REFRENCES

1. Gharti KP, Thapa P, Budhathoki U, Bhargava A. Formulation and in vitro evaluation of floating tablets of hydroxypropyl methylcellulose and polyethylene oxide using ranitidine hydrochloride as a model drug. Journal of Young Pharmacists, 2009; 4(4): 201-208.
2. Aulton ME, Churchill L. Pharmaceutics the science of dosage design. 2nd edition, 2002.
3. Agyilirah GA, Green M, DuCret R, Banker GS. Evaluation of the gastric retention properties of a cross-linked polymer coated tablet versus those of a non-disintegrating tablet. International Journal of Pharmaceutics, 1991; 75: 241–47.
4. Dy ASM, Thom NY. Formulation and evaluation of metronidazole effervescent granules. Int J Pharm Sci Res, 2018; 9: 2525-9.
5. Salim P, Siddaiah M. Formulation and evaluation of effervescent tablets. Journal of Drug Delivery and Therapeutics, 2018; 8(6): 296-303.
6. Rauf P, Monika T, Amit Raj S. Characterization and performance evaluation of HiCel HFS in direct compression tablet formulation, European Journal of Biomedical and Pharmaceutical Sciences (EJBPS), 2024; 11(1): 109-115.
7. Rauf P, Monika T, Amit Raj S. Characterization and performance evaluation of HiCel HFS in direct compression tablet formulation, European Journal of Biomedical and Pharmaceutical Sciences (EJBPS), 2024; 11(1): 109-115.
8. Seema A. Recent development of herbal formulation: A novel drug delivery system. International Ayurvedic Medical Journal, 2014; 6: 953-958.
9. Monika T, Jilika S, Amit Raj S, Singh A.K. Study of microcrystalline cellulose as a substitute of magnesium stearate towards functionality of lubricant in aspirin formulation. International Journal of Development Research, 7(10): 15879-15884.
10. Armin H, Gerhardt. Moisture effects on solid dosage forms formulation processing and stability. Journal of GXP Compliance, 2009; 13: 58-66.
11. United States Pharmacopoeia. General chapter. Bulk density <616>, 40-NF 35, 2018.
12. United States Pharmacopoeia. General chapter. Tapped density <616>, 40-NF 35, 2018.

13. United States Pharmacopoeia. General chapter. Powder flow <1174>, 40-NF 35, 2018.
14. United States Pharmacopoeia. General chapter. Powder flow <1174>, 40-NF 35, 2018.
15. United States Pharmacopoeia. General chapter. Uniformity of dosage units <905>, 40-NF 35, 2018.
16. Aulton ME, Churchill L. Pharmaceutics the science of dosage design. 2nd edition: 2002.
17. Salim P, Siddaiah M. Formulation and evaluation of effervescent tablets. Journal of Drug Delivery and Therapeutics, 2018; 8(6): 296-303.
18. United States Pharmacopoeia. Ascorbic acid tablet monograph, 2018; 2: 2867-2868.
19. Patankar AN, Mandal G. The packing of solid particles. Trans Indian Ceram Soc, 1980; 39(4): 109-119.
20. Aslani A, Jahangiri H. Formulation characterization and physicochemical evaluation of ranitidine effervescent tablets. Adv. Pharm Bull, 2013; 3: 315–322.
21. Roy S, Pare A, Bhattacharjee A, Kesharwani P. Formulation and evaluation of effervescent rizatriptan benzoate tablets for rapid onset of action. Journal of Young Pharmacists, 2013; 5(2): 48-53.