ISSN 2349-7203
IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
HUMAN

Human Journals
Research Article
July 2019 Vol.:15, Issue:4
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Formulation and Evaluation of Directly Compressible Tablets of Furosemide Formulated by Crystallo-Co-Agglomeration

ISSN 2349-7203
IJPPR
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Submission: 21 June 2019
Accepted: 27 June 2019
Published: 30 July 2019

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Crystallo-co-agglomeration, Furosemide, Superdisintegrant, Kawakita plot, Morishima vessel

ABSTRACT

This study aimed to formulate and evaluate directly compressible agglomerates of furosemide with sodium starch glycolate (SSG), crospovidone (CP) and croscarmellose sodium (CCS) respectively, prepared by crystallo-co-agglomeration (CCA) technique. The process of agglomeration involved the use of acetone as a good solvent and chloroform as bridging liquid. The process yielded spherical agglomerates containing ~63% to 91% wt/wt of furosemide. The surface topography of the agglomerates was evaluated by scanning electron microscopy. The agglomerates obtained were evaluated for micrometric, compressibility and drug release properties. The micrometric properties and dissolution characteristics of agglomerates were remarkably improved than that of pure furosemide. The angle of repose for all batches was found between 21.8° to 29.7°. Carr's index was between 5-10 and Hausner's ratio ~1, indicated excellent flowability of agglomerates. The time required for drug release over 60 min, is as F1>F4>F3>F6>F5>F2>F7. Rate of drug release was highest in batch F2 owing to the presence of SSG. The results demonstrate that the CCA of furosemide exhibited improved micrometric properties, compressibility, and dissolution rate.

INTRODUCTION

Direct compression is the preferred method for the manufacturing of tablets owing to its simplicity and process economy. For direct compression, a drug is required to possess good flowability and compressibility(1). Nowadays, various novel techniques such as extrusion-spheronization, melt solidification, melt granulation, melt extrusion and spherical agglomeration have been developed to improve particle properties of drugs having poor flowability and compressibility(2). Spherical agglomeration(3–6) is an agglomeration technique that transforms crystals directly into a compacted spherical form during the crystallization process. However, spherical agglomeration(7,8) technique is suitable for only water-insoluble large-dose drugs as the addition of hydrophilic excipients is difficult with the help of organic bridging liquid.

Crystallo-co-agglomeration (CCA) is a novel technique developed by Kadam *et a.*(9). as an extension of the spherical crystallization that overcomes the limitations of spherical agglomeration and enables for size enlargement of poorly compressible drugs(10–15). In this technique, the drug is simultaneously crystallized and agglomerated with an excipient or with another drug using a bridging liquid(11). This technique has been widely used applied to produce spherical agglomerates with improved micromeritics, mechanical and compressional properties(16–22). The CCA technique has gained popularity because it is carried out in a single step and economic in terms of processing cost.

Furosemide is a diuretic drug having poor flow property and compressibility. It is a poorly water-soluble drug(23) belonging to Class IV of Biopharmaceutical Classification System (BCS). The present study aims to formulate and evaluate the micrometric properties, compressibility, and dissolution of furosemide agglomerates formulated by CCA technique(18). Seven batches of furosemide agglomerates were formulated using sodium starch glycolate (SSG), crospovidone (CP) and croscarmellose sodium (CCS) as agglomerating agents respectively. In this process, furosemide was crystallized from acetone as a good solvent and agglomerated with excipients in the presence of chloroform as bridging liquid(24). The improvement in micrometric properties was determined by calculating the angle of repose, bulk density, tapped density, Hausner ratio, Carr's index of furosemide and its agglomerates respectively. The agglomerates were characterized in the solid-state using techniques such as SEM, FTIR, and dissolution test.

MATERIALS AND METHODS

MATERIALS

Furosemide was procured from Lupin Ltd. All the excipients (Sodium starch glycolate, Crospovidone, and Croscarmellose sodium) and solvents were of analytical grade procured from Dipa chemicals, Aurangabad. The identification test for Furosemide was performed by UV spectroscopic analysis in the range of 220-360 nm using 0.0005% w/v solution in 0.1 M sodium hydroxide. Compatibility of Furosemide and excipients were analyzed by the FTIR spectroscopic technique. The compatibility was analyzed as a physical mixture of Furosemide with sodium starch glycolate (SSG), crospovidone (CP), croscarmellose sodium (CCS) and microcrystalline cellulose (MCC) respectively.(25)

METHODS

Crystallo-Co-Agglomeration

The process of agglomeration involves the use of acetone as a good solvent and chloroform as bridging liquid. Three super disintegrants i.e. sodium starch glycolate (SSG), crospovidone (CP) and Croscarmellose sodium (CCS) were used as agglomerating agents owing to their water insolubility. The agglomerates were prepared using the super disintegrant composition given in Table 1. A solution of Furosemide was prepared in good solvent i.e. acetone (1 g in 5 mL solvent) and heated to about 40°C. A one-third portion of the super disintegrant was added to this solution, which was then added immediately with stirring to the bad solvent placed in a modified vessel for agglomeration maintained at temperature 0-5°C using an ice bath. Bad solvent consists of the two-third part of the super disintegrant, HPC (10% w/w of drug+superdisintegrant) and PEG 6000 (6.5% w/w total solid content) to provide a suitable medium for agglomeration. The solution of the drug in the good solvent is added to the bad solvent with stirring to ensure proper mixing of the media. The bridging solvent was added in a drop-wise manner to form proper agglomerates of the drug. Seven batches (F1-F7) of agglomerates were prepared and evaluated. F1 batch served as the control batch in which super disintegrant was not added.

Yield and Drug Content

Agglomerates were weighed after drying and process yield was calculated. The yield of the agglomerates obtained by F1-F7 was calculated. Drug content of the agglomerates was determined by extracting 50 mg of agglomerates in 50 ml phosphate buffer pH 5.8. The

solution was filtered to remove undissolved material and analyzed using UV spectroscopic method. The drug content in 50 mg of agglomerates was determined for all seven batches.

Surface Topography

Photomicrograph of drug particles was taken by OLYMPUS microscope (model CX31) fitted with a camera. The agglomerates were photographed at original magnification × 22.5 and Shape factor (S) was calculated from Area (A) and Perimeter (P) obtained from tracings of enlarged photomicrographs of agglomerates with the aid of MAGNUS PRO software.

Table No. 1: Polymer composition for furosemide agglomeration

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7
Furosemide	1000	1000	1000	1000	1000	1000	1000
SSG	-	100	200	-	-	-	-
CP	-	-	-	100	200	-	-
CCS	-	-	-	-	-	100	200
HPC	100	110	120	110	120	110	120
PEG 6000	71.5	78.65	85.8	78.65	85.8	78.65	85.8
Total weight	1171.5	1289	1406	1289	1406	1289	1406

Surface morphology of the agglomerates was analyzed by scanning electron microscopy (Diya Lab, Navi Mumbai).

Micromeritic Properties

The agglomerates were evaluated for flowability by fixed funnel method and micromeritic parameters such as bulk density, tapped density, Carr's index, and Hausner’s ratio were calculated. Compressibility was calculated with the help of Kawakita plot.

Table No. 2: Formulation of directly compressible tables of furosemide

Ingredients (mg)	Batch						
	F1	F2	F3	F4	F5	F6	F7
Amount of agglomerates equivalent to 40 mg of the drug	43.69	63.01	49.6	53.36	50.82	50.31	53.07
Microcrystalline cellulose	83.81	64.49	77.9	74.14	76.68	77.19	74.43
Talc	15	15	15	15	15	15	15
Magnesium stearate	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Total weight	150	150	150	150	150	150	150

Weight variation

Directly compressible tablets were formulated as per the formulae are given in Table 2. Five tablets were prepared from each batch. Weight variation test was performed according to the United States Pharmacopoeia. Weight of all five tablets from each batch was recorded and weight variation was calculated. Hardness was evaluated by Monsanto and Pfizer hardness tester (Table 9).

Disintegration and Dissolution Studies

Disintegration studies were performed using a standard disintegration test apparatus (Make: Scientific, Model: Microprocessor disintegration test apparatus, Location: Government College of Pharmacy, Aurangabad). The dissolution studies were performed using United States Pharmacopeia (USP) type 2 dissolution test apparatus (DA-6, Veego Scientific, Mumbai, India). The dissolution medium used was Phosphate buffer pH 5.8 and the paddle speed was 50 rpm. Samples were collected for 1 hour.

RESULTS AND DISCUSSION

Identification of furosemide by UV Spectroscopy

UV spectroscopy of furosemide(26) in 0.1M NaOH exhibited λ_{max} at 269nm and principle absorption peaks at 330nm and 269nm (Figure 1a). The λ_{max} matches with the Indian Pharmacopoeial standard.

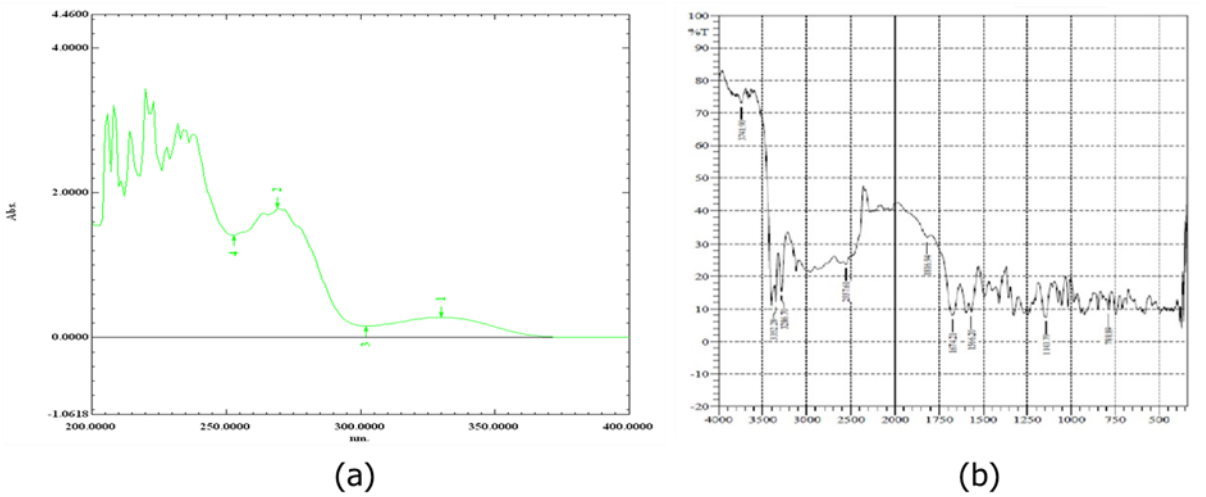

Figure No. 1: (a) UV Spectrograph of Furosemide (0.1M NaOH solution), (b) FTIR of furosemide

Drug-excipient compatiblity by FTIR

The principle absorption peaks observed in FTIR analysis of furosemide (1b) and physical mixtures of furosemide with SSG, CP, CCS and MCC (Figure2a-d) are summarized in Table 3. The FTIR spectra indicate that furosemide is compatible with the excipients used in the study.

Table No. 3: Interpretation of FTIR Spectra of furosemide with SSG, CP, CCS and MCC (2a-d)

Functional group	Peak value	Drug	Drug+ SSG	Drug+ CP	Drug + CCS	Drug + MCC
CH stretching	3050-3150	3150	3105	3085	3120.82	3120.82
OH stretching	2500-3500	2557.2	2850	2872.01	2872	2765
NH stretching	3300-3500	3352	3480	3348.42	3398.57	3400.82
CONH	1630-1680	1674.2	1693.5	1672.28	1668.43	1676.14
S=O	1000-1100	1030	1083.93	1074.28	1050	1090
C=N	1640-1690	1674.21	1680	1660	1650	1670
Aromatic ring	600-900	788	830	748.38	742.59	746.45

Characterization of agglomerates by SEM

SEM shows that pure furosemide crystals have a needle-like surface (Figure 3a). Furosemide agglomerates show the spherical structure of agglomerates (Figure 3b). The agglomerates were spherical with shape factor values near unity. SEM revealed that closely packed agglomeration of the drug has occurred over the surface of the drug (Table 4).

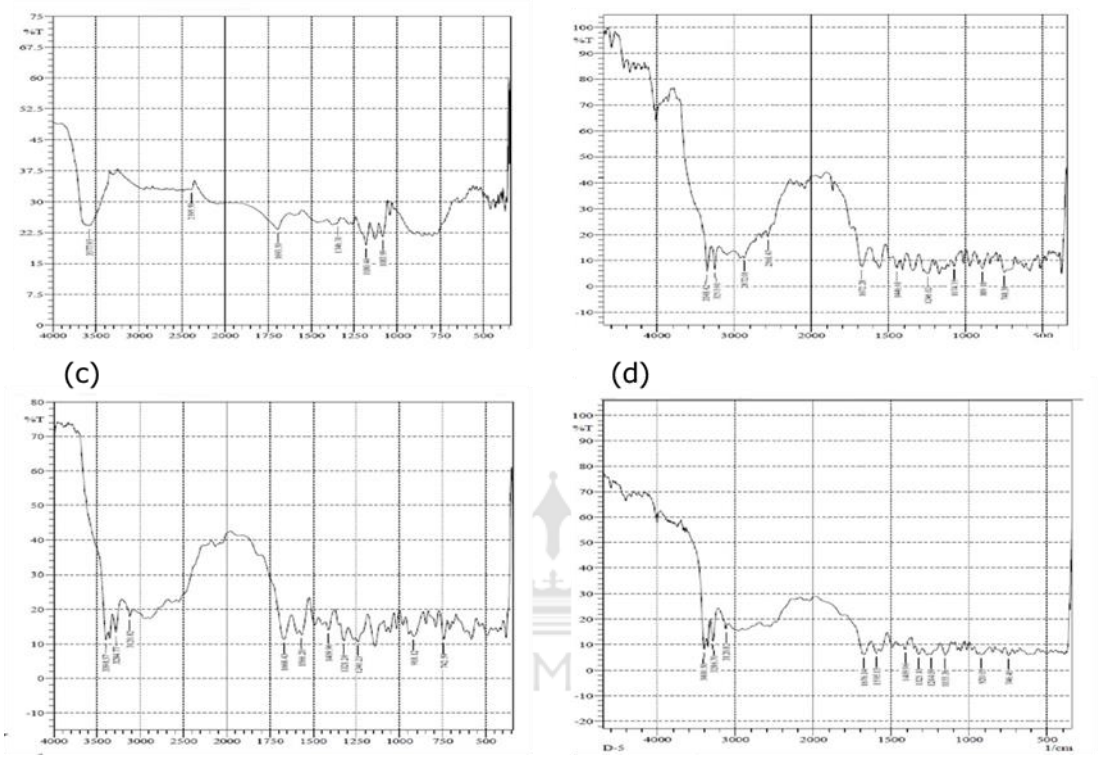

Figure No. 2: FTIR spectra of furosemide with (a) SSG, (b) PVP, (c) CCS, and (d) MCC

Table No. 4: Shape factor of agglomerates (F1-F7)

Batch	Shape Factor
F1	0.9994
F2	0.9995
F3	0.999
F4	0.9994
F5	0.9994
F6	0.9994
F7	0.9994

Process yield and drug content

For F1, F2, F3, F4, F5, F6 and F7, the yield of agglomerates was 72.55% w/w, 57.79% w/w, 78.09% w/w, 75.09% w/w, 89.40% w/w, 57.56% w/w, 92.6 % w/w respectively. The drug content of agglomerates was 91.54% w/w, 63.48% w/w, 80.64% w/w, 74.96% w/w, 78.70% w/w, 79.50% w/w and 75.36% w/w respectively.

Table No. 5: Percent yield and drug content of furosemide agglomerates (F1-F7)

Batch	Weight of agglomerate (mg)	% Yield	% Drug content
F1	850	72.55	91.54
F2	745	57.79	63.48
F3	1098	78.09	80.64
F4	968	75.09	74.96
F5	1257	89.40	78.70
F6	742	57.56	79.50
F7	1302	92.60	75.36

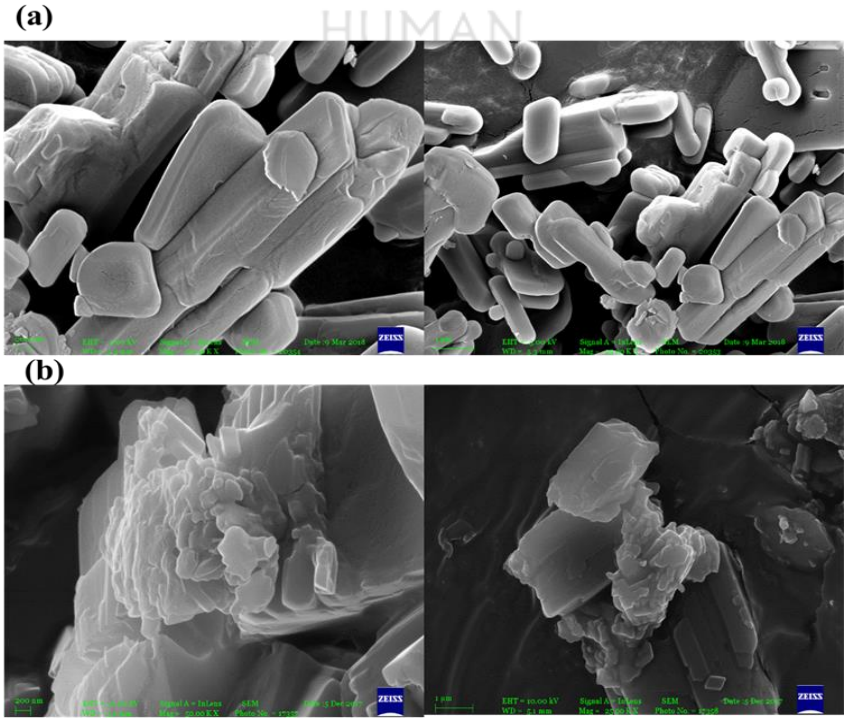

Figure No. 3: SEM photomicrograph of (a) furosemide (Magnification: 50.0KX/25.0KX) (b) furosemide agglomerates (F4) (Magnification: 50.0KX/25.0KX)

Pre-compressional evaluation

Pre-compressional evaluation of agglomerates for the angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio revealed the excellent flow properties of agglomerates (Table 6).

Table No. 6: Pre-compressional evaluations of Agglomerates

Batch	Angle of repose (^{0})	Bulk Density (g/cc)	Tapped density (g/cc)	Carr's index (%)	Hausner ratio
F1	21.8	0.41	0.44	5.55	1.05
F2	27.2	0.37	0.41	10.0	1.11
F3	29.7	0.37	0.41	10.0	1.11
F4	26.8	0.50	0.53	6.66	1.07
F5	27.0	0.39	0.41	5.26	1.05
F6	26.1	0.44	0.46	5.88	1.06
F7	27.5	0.37	0.39	5.00	1.05

Compressibility

Compressibility of the agglomerates was evaluated by Kawakita plot (Figure 4). To comply with data of drug, **a** value of the sample should be more than **a** value of the drug and **1/b** value should be less than that of the drug(27). Batch F2, F5 and F7 comply with all the conditions of constants and therefore it was concluded that compressibility is improved in all these batches (Table 7).

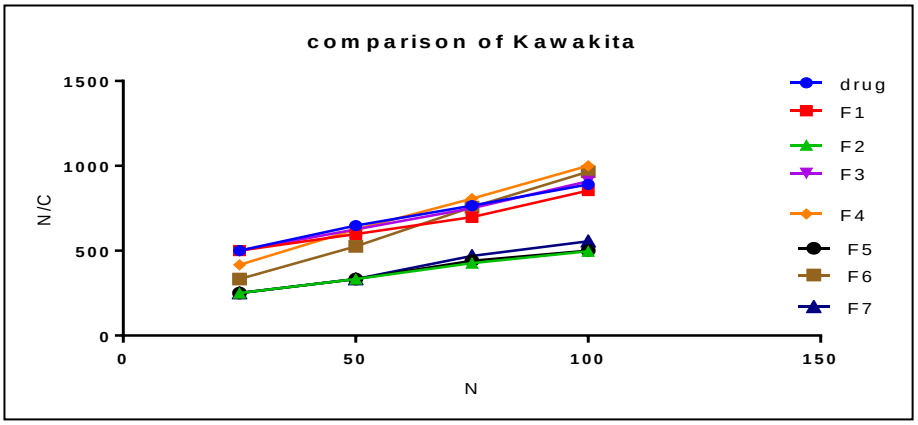

Figure No. 4: Kawakita plot of furosemide and Seven batches (F1-F7) of agglomerates

Table No. 7: Kawakita plot analysis F1-F7

Batch	Equation of line	R2	A	1/b	Ab
Drug	Y= 5.148x+379	0.997	0.194	73.526	0.00264
F1	Y= 4.655x+371.61	0.985	0.214	79.52	0.00268
F2	Y= 3.3396x+168	0.9975	0.2994	50.29	0.00595
F3	Y= 5.4091x+357.96	0.996	0.1848	66.15	0.0027
F4	Y= 7.7266x+229.1	0.993	0.1294	29.64	0.0043
F5	Y= 3.4315x+166.65	0.988	0.291	48.57	0.00599
F6	Y= 8.512x+113	0.998	0.117	13.26	0.0088
F7	Y= 4.2076x+138.9	0.99	0.2376	33.04	0.0077

Dissolution and Disintegration studies

The release of drug from agglomerates was more than 83.14%, within 60 min. Drug release from agglomerates F1, F2, F3, F4, F5, F6 and F7 was 75.92%, 89.92%, 78.03%, 77.78%, 88.99%, 81.36% and 89.98% respectively. Dissolution study of directly compressed tablets prepared from agglomerates showed that release of drug was significantly faster for batches F2,F5, and F7 than F1, F3, F4 and F6 (Table 8). Moreover, the release rate was found to be improved as compared to the conventional marketed formulation(28). Disintegration time was found to increase as the concentration of super disintegrants increases as evident from batch F5 and F7 (Table 9). Comparative disintegration and hardness profile of F1-F7 indicates that there is no significant effect of hardness of agglomerates on disintegration time (Table 9).

Table No. 8: Comparative dissolution profile (F1-F7)

Time	% Drug release							
	F1	F2	F3	F4	F5	F6	F7	Marketed formulation
0	0	0	0	0	0	0	0	0
5	26.43	48.69	31	36.15	6.08	27.24	29.38	39.18
15	30.06	51.46	41.07	42.06	29.2	31.67	46.79	46.17
30	47.34	66.41	58.32	53.34	42.89	46.01	65.99	68.03
45	59.55	71.91	71.84	61.57	73.79	59.02	81.06	76.11
60	75.92	89.92	78.03	77.78	88.99	81.36	89.98	87.31

Table No. 9: Comparative disintegration and hardness profile of F1-F7

Batch	The average weight of tablet (mg)	Hardness (Kg/cm^2)	Disintegration time
F1	148.4	3	>5 min
F2	149.2	4	2 min 50s
F3	151.8	3.5	1 min 45s
F4	149.4	4.2	1 min 55s
F5	151.4	3.8	1 min 25s
F6	150.356	4	1 min 30s
F7	150.3	3.8	45 s

CONCLUSION

In the present study, the CCA method was developed to obtain directly compressible agglomerates of furosemide with excipients. The pre-compression studies revealed that CCA of furosemide formulated with SSG, CP, CCS, and MCC exhibited improved micrometric and compressibility properties. Post-compression studies demonstrated improvement in the disintegration and dissolution rate due to agglomeration. This technique can be applied for producing directly compressible oral solid dosage forms of furosemide with improved compressibility and dissolution rate. It can be concluded that flowability, compressibility and tableting properties of furosemide can be enhanced by crystallo-co-agglomeration technique.

ACKNOWLEDGMENT

The authors are thankful to the Government College of Pharmacy Aurangabad for infrastructure and research facility.

REFERENCES

1. Dokala GK, Pallavi Ch. Direct Compression-An Overview. Int. J. Res. Pharm. Biomed. Sci. 2013; 4(1):155–8.
2. Keshwani B, Jaimini M, Sharma D. Spherical crytallization: A revolution in the field of particle engineering. Int J Curr Pharm Res. 2010;7(4):19–25.
3. Kawashima Y, Imai M, Takeuchi H, Yamamoto H, Kamiya K, Hino T. Improved flowability and compactibility of spherically agglomerated crystals of ascorbic acid for direct tableting designed by spherical crystallization process. Powder Technol. 2003;130(1-3):283–9.
4. Gupta MM, Srivastava B, Arya V. Spherical Crystallization: A Tool Of Particle Engineering For Making Drug Powder Suitable For Direct Compression. Int J Pharm Res Dev. 2010;1(12):1–10.

5. Viswanathan CL, Kulkarni SK, Kolwankar DR. Spherical agglomeration of mefenamic acid and nabumetone to improve micromeritics and solubility: A technical note. AAPS PharmSciTech. 2006;7(2):E122–5.
6. Paradkar AR, Pawar AP, Chordiya JK, Patil VB, Ketkar AR. Spherical crystallization of celecoxib. Drug Dev Ind Pharm. 2002;28(10):1213–20.
7. Kovačič B, Vrečer F, Planinšek O. Spherical crystallization of drugs. Acta Pharm. 2012;62(1):1–14.
8. Bhadra S, Kumar M, Jain S, Agrawal S, Agrawal GP. Spherical crystallization of mefenamic acid. Pharm Technol. 2004;28(2):66–76.
9. Kadam SS, Mahadik KR, Paradkar AR, inventors. A process for making agglomerates for use as or in a drug delivery system. Indian patent 183036. February 14, 1997.
10. Chaturvedi A, Sharma K, Bansal M. A Review on Recent Advancement in Crystallo-co-Agglomeration. Adv Biol Res (Rennes). 2011;5(6):273–81.
11. Paradkar A, Pawar A, Jadhav N. Crystallo-co-agglomeration: A novel particle engineering technique. Asian J Pharm. 2010;4(1):4.
12. G Prajapati B. Crystallo co agglomeration" The Novel Approach For Microparticulation. Res Rev Healthc Open Access J. 2018;1(3).
13. Rahate NB, Bodhankar MM, Dhoke PN. Crystallo-Co-Agglomeration: A Novel Technique To Improve Flow And Compressibility. J Drug Deliv Ther. 2016;3(4):178-183.
14. Rahate NB, Mitali B, Priyanka D. crystallo-co-agglomeration: a novel technique to improve flow and compressibility. J Drug Deliv Ther. 2013;3(4):178–83.
15. Shen R, Shan L, Gao C. Advance on crystallo-co-agglomeration based particle engineering technique. Chin. Pharm. J. 2014;49(17):1481–5.
16. Pawar A, Paradkar A, Kadam S, Mahadik K. Agglomeration of ibuprofen with talc by novel crystallo-co-agglomeration technique. AAPS PharmSciTech. 2005;5(4):30–5.
17. Yadav AA, Yadav DS, Karekar PS, Pore Y V, Gajare P. Enhanced solubility and dissolution rate of Olmesartanmedoxomil using crystallo-co-agglomeration technique. Pelagia Res Libr. 2012;3(2):160–9.
18. Kadam AM, Patil SS. Improvement Of Micromeritic, Compressibility And Solubility Characteristics Of Linezolid By Crystallo-Co-Agglomeration Technique. Int J Appl Pharm. 2017;9(4):47-53.
19. Chatterjee A, Shrivastava B, Sharma GN, Mohan Gupta M. Crystallo-co-agglomeration of Valsartan for Improved Solubility and Powder Flowability. Asian J Pharm. 2018;12(3):182-195.
20. Chandran CS, Theju JT, Vipin K V, Amitha S. Crystallo-co-agglomeration: an effective tool to change the powder characteristics of Indomethacin IP. Int J Pharm Pharm Res. 2016;5(4):197–207.
21. Jadhav N, Pawar A, Paradkar A. Design and evaluation of deformable talc agglomerates prepared by crystallo-Co-agglomeration technique for generating heterogenous matrix. AAPS PharmSciTech. 2007;8(3):E61–7.
22. Maghsoodi M, Taghizadeh O, Martin GP, Nokhodchi A. Particle design of naproxen-disintegrant agglomerates for direct compression by a crystallo-co-agglomeration technique. Int J Pharm. 2008;351(1–2):45–54.
23. Ghadi R, Dand N. BCS class IV drugs: Highly notorious candidates for formulation development. J. Controlled Release 2017;248:71–95.
24. Kawashima Y, Lin SY, Naito M, Takenaka H. Direct agglomeration of sodium theophylline crystals produced by salting out in liquid. Chem. Pharm. Bull. 2011;30(5):1837–43
25. Rowe, Raymond C; Sheskey PJFME. Handbook of Pharmaceutical Excipients. 6th ed. London: American Pharmacists Association. 2012.
26. Dias ILT, Martins JLS, De Neto GO. Furosemide determination by first-derivative spectrophotometric method. Anal Lett. 2005;38(7):1159–66.
27. Mazel V, Busignies V, Duca S, Leclerc B, Tchoreloff P. Original predictive approach to the compressibility of pharmaceutical powder mixtures based on the Kawakita equation. Int J Pharm. 2011;410(1–2):92–8.
28. Yu LX, Wang JT, Hussain AS. Evaluation of USP apparatus 3 for dissolution testing of immediate-release products. AAPS PharmSci. 2002;4(1):1–5.