International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1496-1503www.ijprajournal.com ISSN: 2249-7781

Enhancement of Solubility of Furosemide Utilizing Different Techniques of Inclusion Complex

SujanNeupane[1, 2,] SubodhChataut[2]NavrajUpreti[2, 3] Devendra KumarNeupane[3]
[1] *Valley College of Technical Sciences, Sitapaila, Kathmandu, Nepal*
[2]*Department of Drug Administration, Bijulibajar, Kathmandu, Nepal*
[3]*Nepal Institute of Health Science, Gokarneshwor, Jorpati, Kathmandu, Nepal*
** Corresponding Author: SujanNeupane, Pharmacy Officer, Department of Drug Administration, Bijulibajar, Kathmandu, Nepal*

Submitted: 15-05-2023 Accepted: 30-05-2023

ABSTRACT:
Furosemide,highly hydrophobic drug, is a potent high ceiling loop diuretic classified as BCS classIV drug having low solubility and low permeability. Furosemide isincompletely or slowly dissolved in the gastrointestinal tract absorbed orally over 2-3hours and has 60% bioavailability for oral route. The aim of the study is to formulate and investigate the inclusion complex of Furosemide by different techniquesviz direct mixing, solvent evaporation and kneading method as a potential method to increase bioavailability along with a vision of the comparative study of those methods. Preparedinclusion complex tablets of Furosemide utilizes urea as key polymer in different ratios to increase the dissolution rate. All the powderblends were evaluated for pre-compression parameters like bulk density, tappeddensity, Hausner ratio, Carr index and angle of repose and showed the acceptable flowproperties. Post-compression parameters like weight variation, hardness, thickness, friability and disintegration time were found to be within specified limits. The optimized formulation KF1 prepared by kneading method showed the % drug release of 91.175% at the end of 240 minutes.

KEYWORDS: Furosemide, inclusion complex, solubility, direct mixing, solventevaporation, kneading.

I. INTRODUCTION

[1] Oral route of drug administration is the most usual method of delivering drug. Drugs which are administered orally gets completely absorbed and shows good bioavailability when they show fair solubility in gastric medium.The solubility and dissolution properties of drugs are crucial parameters for formulation development. [2] To be pharmacologically active, the drug must permeate the biological membranes via passive diffusion just as lipophilic drugs do. Poorly water soluble compounds show dissolution rate limited absorption and hence insufficient bioavailability.

[3] Therefore, the enhancement of solubility is the major challenging aspect for oral drug delivery system for better enhancement of the oral bioavailability. Various techniques such as particle size reduction, nanosuspension, use of surfactants, salt formation,complexation, solid dispersion, etc. has been adapted for the enhancement of solubility of poorly soluble drugs.[4, 5] A variety of methods can be enforced to boost the aqueous solubility of poorly soluble drugs one of which is the usage of solubilizing complexing agents.Complexation is aunique technique used to increase solubility,dissolution and bioavailability of poorly watersoluble drugs. The alliance of two or more molecules initiate a non-covalent complex with higher solubility than the drug is the major objective of developing the inclusion complex.[6] Inclusion complex generally contain two molecule one is host and another is a guest molecule. Hydrophobic part of the guest molecule can easily fit into the cavity of host molecule. Such systems reach into the systemic circulation by passive diffusion. Polymers form complex with the drug molecule by putting up into the cavity. The distinctive characteristic of inclusion complex encompasses faster dissolution rate, and shorterdrug release time, and also more efficient absorption which implies improved oral bioavailability, increasing biological activity, which prompt reduction of drug dosage.

[7-9] Furosemide is a BCS class IV drug with low solubility and low permeability. It is a real challenge to enhance the solubility of drug. Furosemide is a potent high ceiling loop diuretic. It has plasma half-life of 6-8 hours.Furosemide is antidiuretic drug. It is inhibitor of Na^+ K^+ $2Cl^-$ cotransport.FDA approved the use of loop diuretics alone or in combination with other hypertensive medications as an alternative to thiazide diuretics to

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1496-1503www.ijprajournal.com ISSN: 2249-7781

treat hypertension.Furosemide can be a second-line agent in heart failure patients with symptoms and patients with advanced kidney disease with an estimated glomerular filtration rate, less than 30 ml per minute the loop diuretics (Furosemide) are preferred over thiazide diuretics to treat hypertension.The bioavailability and aqueous solubility of the Furosemide is poor when it is given orally.

Therefore, there is a need to develop inclusion complex of Furosemide. The basic goal of designing inclusion complex of Furosemide is to reduce drug hydrolysis, enzymatic decomposition, odor, and taste and enhance bioavailability. The drug is mixed with various polymers to control the drug release.

In this study, an attempt was made to improve thesolubility and dissolution rate of Furosemide bycomplexing with Urea, therebyincreasing its bioavailability and therapeuticsefficiency. In addition this study also highlights on the best suitable methods for the formulation of inclusion complexes of Furosemide.

II. MATERIALS & METHODS

1.1 Materials

Furosemide was obtained as gift sample from National Healthcare Pvt. Ltd., Chhatapipra, Bara,Nepal. All the other chemicals and reagents were of analytical grade.

1.2 Methods

1.2.1 [10] Calibration Curve: 10 mg of the pure drug was accurately weighed and dissolved in 10 ml methanol, and the volume was made up to 10 ml with methanol to give a standard stock solution of 1000 µg/ml. Further 1000 ppm withdrawn 2.5 ml of Aliquote diluted to 25 ml of volumetric flask and prepare 100 ppm and Suitable dilutions were made with distilled water to get standard solutions of concentration: 5,10,15,20,25 µg/ml at 277 nm.

1.2.2 [11-13] Pre formulation studies:

a. Color and Appearance: The sample was observed visually.

b. Solubility studies: Solubility studies of Furosemide were carried out in water, phosphate buffer pH 5.8 and polyethene glycol (PEG 400). Saturated solutions were prepared by adding an excess drug to the vehicle and shaking in a water bath with a shaker for 48h at 25±0.5 °C under constant vibration. After this period the solutions were filtered, diluted and analyzed by UV spectrophotometer at 277 nm. Three determinations were carried out for each sample to calculate the solubility of Furosemide.

c. Bulk density (Db): It is the ratio of total mass of powder to the bulk volume of powder. Required quantity of powder blend was transferred in 100 ml graduated cylinder and the bulk density was calculated by using the formula given below:

Db=W/Vb

Where,

W= Mass of powder

Vb= Bulk volume of the powder

d. Tapped density (Dt): It is the ratio of total mass of powder to the tapped volume of powder. Required quantity of powder blend was transferred in 100 ml graduated cylinder which was operated for fixed number of taps until the powder bed volume has reached a minimum Tapped density using the was calculated by formula given below:

Dt =W/ Vt

Where,

Dt= Tapped density

W= Weigh of powder

Vt= Tapped volume

e. Compressibility/Carr's Index: It is a simple test to evaluate bulk and tapped density of a powder. The formula for Carr's index is as below:

Compressibility index = 100 x TD - BD/TD

f. Hausner's Ratio: Hausner's ratio is a number that is correlated to the flow ability of a powder.

Hausner's Ratio = BD/ TD

g. Angle of Repose:It is the maximum angle possible between the surface of a pile of powder and the horizontal plane. Angle of repose was determined by the funnel method. Accurately weighed powder blend was taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured, and angle of repose was calculated using the given formula.

$\theta = \tan^{-1}(h/r)$

Where,

θ = angle of repose

h = height in cms,

r = radius in cms

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1496-1503www.ijprajournal.com ISSN: 2249-7781

1.2.3 [14-19] Preparation of inclusion complex of Furosemide:

a. Direct compression (DF1-DF3): Direct compression is the simplest and most economical method for the manufacturing of tablets because it requires fewer processing steps than other techniques. In this technique tablets are compressed directly from powder blends of active ingredient and excipients, which flow uniformly in the dies and forms a film compact.
b. Solvent evaporation (SF1-SF3): This method involves dissolving of the drug and urea separately in to two mutually miscible solvents, mixing of both solutions to get molecular dispersion of drug and complexing agents and evaporating the solvent by heating in water bath at 45ºC to obtain solid powdered inclusion compound. The dried mass was pulverized and passed through No.80 sieve.
c. Kneading method (KF1-KF3): Weighed quantity of urea was mixed with minimum quantity of distilled water in a mortar to obtain a homogeneous paste. Weighed quantity of drug powder was then added slowly. The mixture was then grounded for 1 h. During this process, an appropriate quantity of water was added to the mixture to maintain a suitable consistency. The whole procedure was carried out at room temperature. The paste was dried in oven at 45°C for 24 h. The dried complex was pulverized and passedthrough No. 80 sieve.

Ingredients	DF1	DF2	DF3	SF1	SF2	SF3	KF1	KF2	KF3
Furosemide	40	40	40	40	40	40	40	40	40
Urea	20	40	60	20	40	60	20	40	60
Stearic Acid	4	4	4	4	4	4	4	4	4
Starch	20	20	20	20	20	20	20	20	20
Sodium Alginate	10	10	10	10	10	10	10	10	10
MCC	40	40	40	40	40	40	40	40	40
Talc	6	6	6	6	6	6	6	6	6
Mannitol	60	40	20	60	40	20	60	40	20
Total weight in mg	200	200	200	200	200	200	200	200	200

Table 1: Formulation Table for Preparation of Inclusion Complex of Furosemide

1.2.4 [20-22] Post-compression parameters:

a. Weight Variation: 10 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not.

% $weigh\,tvariation = Averageweigh\,t - weigh\,tofeacttablet/\ Averageweigh\,t$ * 100%

b. Hardness Test: Hardness of tablet is defined as the force applied across the diameter of the tablet to break the tablet. The hardness of the tablets was determined by diametric compression using Monsanto hardness tester.
c. Thickness:The thickness was measured by placing tablet between two arms of the vernier calipers. Three tablets were taken, and their thickness was measured.
d. Friability Test: This test was performed to determine the effects of friction and shock. Pre weighed sample of 10 tablets was placed in the Roche friabilator and rotated at 25 rpm. The tablets were dedusted and reweighed, and the friability percentage was calculated. Compressed tablets should not lose more than 1% of weight.

% $Friability = Initialweigh\,t - Finalweigh\,t/\ Initialweigh\,t*$ 100

e. In-Vitro Disintegration Test:The in vitro disintegration studies were carried out using a digital tablet disintegration test apparatus. One tablet was placed in each of the 6 tubes of the basket assembly and then disk was added to each tube. This assembly was then suspended in a 1-liter beaker containing water with its temperature beingmaintained at 37±2°C. The basket was then moved up and down through a distance of 5 to 6 cm, at the frequency of some cycles per minute. The time required for complete disintegration of the tablet was recorded.
f. In-Vitro Dissolution Studies: The release rate of 40mg Furosemide was determined by using dissolution testing apparatus II (paddle method). Dissolution test was performed using 900ml of 0.1N HCl pH 1.2 as a dissolution medium at 37±0.5°C which was stirred with a rotating paddle at 50 rpm. A sample 5ml of the solution was withdraw

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1496-1503www.ijprajournal.com ISSN: 2249-7781

from the dissolution apparatus at 0.5, 1, 2, 3, 8 hours and analyzed at 277nm using UV spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

III. RESULTS

1.3 Characterization

1.3.1 Color and Appearance: The drug was almost white crystalline powder.

1.3.2 Solubility: Soluble in acetone, sparingly soluble in ethanol (96%), practically insoluble in methylene chloride it dissolves in dilute solution of alkali hydroxides.

1.3.3 Standard Calibration Curve:

Concentration (µg/ml)	Absorbance
0	0
5	0.1922
10	0.5357
15	0.8327
20	1.133
25	1.4018

Table 2: Calibration data of Pure Drug

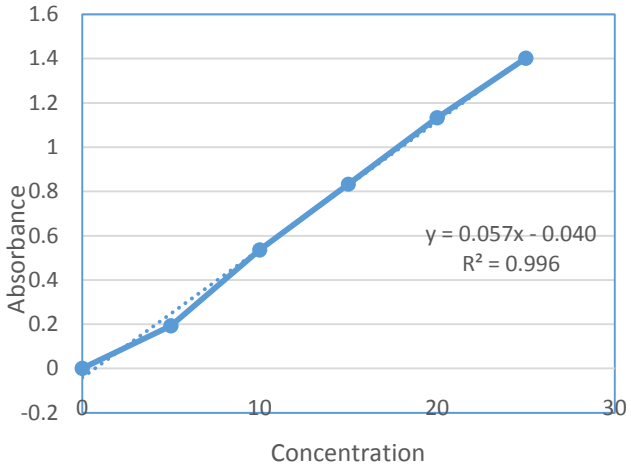


Fig1: Calibration Curve of Allopurinol

1.4 Pre-compression Parameters:

The powder blends obtained by various methods before formulation into the tablets were evaluated for pre-compression parameters, which shows the data as depicted in Table 3. Powder blends were subjected for density evaluation, compressibility index determination and for the type of flow.

Formulation Code	Loose density (g/ml)	Tapped bulk density (g/ml)	Hausner Ratio	Compressibility index	Angle of Repose
DF1	0.65±0.086	0.82±0.040	0.72±0.031	28±3.605	37.25±1.947
DF2	0.62±0.034	0.79±0.051	0.79±0.029	20.8±3.288	33.59±1.214
DF3	0.5±0.090	0.91±0.144	0.55±0.038	44.6±4.26	33.59±1.214
SF1	0.506±0.144	0.916±0.144	0.553±0.317	44.6±4.25	33.42±1.647
SF2	0.833±0.144	1.16 ±0.288	0.723±0.319	27.77±3.62	32.55±1.214
SF3	0.62 ±0.034	0.793±0.051	0.793±0.028	21.88±3.42	33.59±0.782
KF1	0.499±0.046	0.7±0.086	0.645±0.030	35.424±3.66	28.37±2.563
KF2	0.53±0.057	0.833±0.144	0.655±0.032	34.44±3.68	33.74±0.511
KF3	0.533±0.057	0.91 ±0.144	0.6±0.031	40±4.68	25.94±0.531

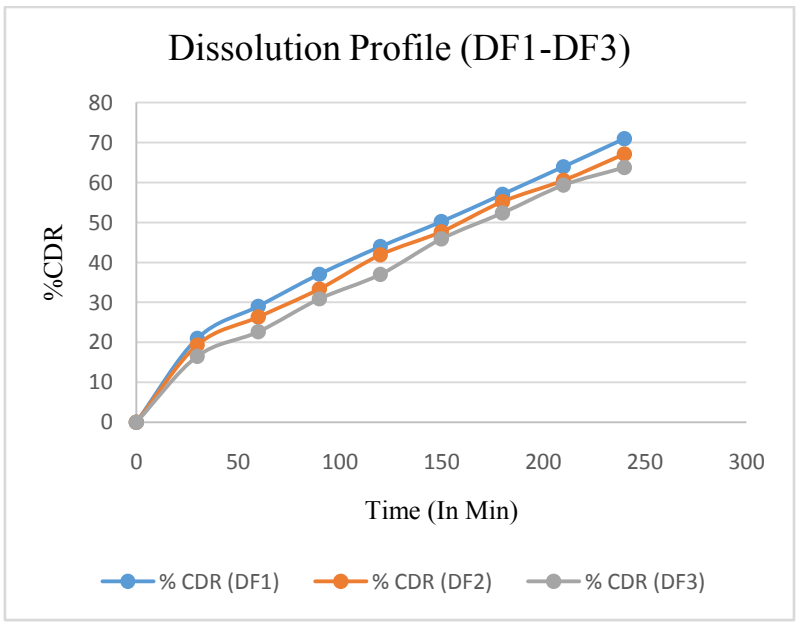
Table 3: Pre-compression Parameters Study Data of Powder Blend

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1496-1503www.ijprajournal.com ISSN: 2249-7781

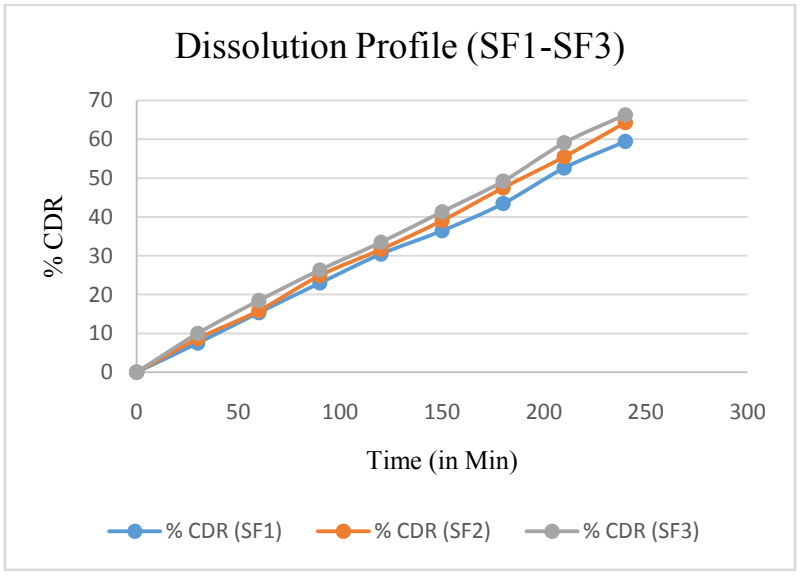
1.5 Post-compression Parameters:

All the tablets formulations were evaluated for various parameter such as hardness, friability, thickness, weight variation, in-vitrodissolution studies and analysis of dissolution data, in-vitro test determination. The obtained data is shown in the table below:

Formulation Code	Thickness (mm)	Hardness (kg/cm^3)	Friability (%w/w)	Weight variation (g)	Disintegration time (In min)
DF1	0.34±0.19	4.16±0.288	0.54±0.045	0.197±0.004	4.5±0.087
DF2	0.34±0.05	1.83±0.416	0.72±0.043	0.196±0.004	4.38±1
DF3	0.33±0.11	3.83±0.286	0.26±0.04	0.1994±0.039	4.60±1.03
SF1	4.46±1.76	3±0.5	0.187±0.045	0.197±0.048	4.21±1.01
SF2	3.36±0.05	3±0.5	0.187±0.045	0.2005±0.004	3.86±0.65
SF3	3.4±0.1	3.8±1.408	0.283±0.043	0.1986±0.004	3.85±0.64
KF1	3.3±0.1	3.46±0.05	0.1±0.039	0.198±0.046	1.346±0.157
KF2	3.63±0.208	3.23±0.27	0.20±0.048	0.198±0.046	2.40±1.4
KF3	3.367±0.11	2.76±0.64	0.27±0.041	2±0.004	2.32±0.119



International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1496-1503www.ijprajournal.com ISSN: 2249-7781



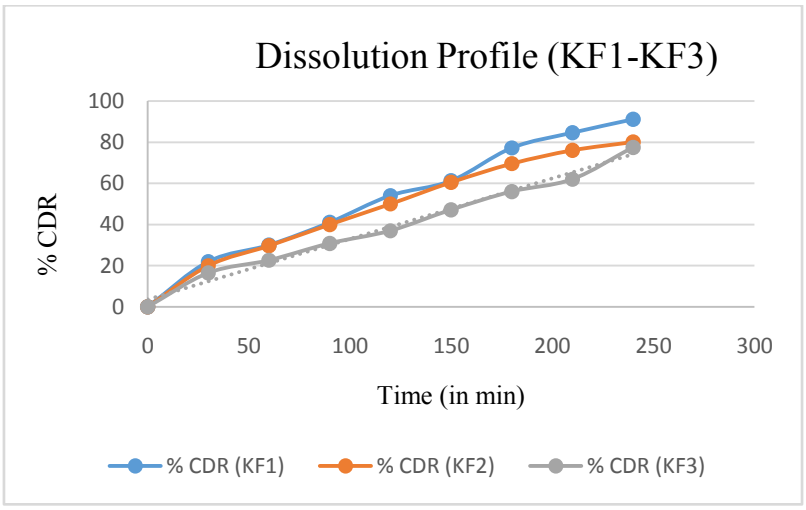


Fig 2: Dissolution Profiles (DF- Direct Compression Formulation; SF- Solvent Evaporation Formulation; KF- Kneading Method Formulation)

IV. DISCUSSION AND CONCLUSION

Furosemide is poorly soluble in water and its bioavailability and aqueous solubility is poor, therefore, there is a need to develop inclusion complexes of Furosemide. Inclusion complex of Furosemide were successfully prepared by utilizing three different techniques namely direct compression, solvent evaporation, kneading method using various concentration of polymer (Urea). Various excipients are used for aforementioned techniques such as stearic acid, starch, MCC, mannitol, ethanol etc. Pre-compression and post-compression parameters were evaluated as prescribed by the pharmacopoeias.Pre and post- compression studies showed that all the formulations were within the pharmacopoeiallimits. The formulated tablets showed compliance with various physic-chemical parameters, hardness, friability, etc.

V. SUMMARY

Inclusion complex of Furosemide was prepared using three different techniques in different ratios of polymer. Three different formulations were prepared in each techniques. DF1-DF3 indicates the formulations were prepared using Direct Compression Technique; SF1-SF3 denotes Solvent Evaporation Technique and KF1-

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1496-1503www.ijprajournal.com ISSN: 2249-7781

KF3 implies Kneading Method. Inclusion complex of Furosemide was prepared with an intention of increasing the solubility and dissolution rate which will in turn increase the bioavailability. Among all the formulations, KF1 showed the superior result when compared with other formulations. It showed the friability of 0.1% with a disintegration time of 1.34 minutes. The formulation KF1 showed a release of 91.17% at the end of 8 hours making it the optimized formulation. In addition to this, kneading method was proven to be a better method than direct compression and solvent evaporation method for the formulation of inclusion complex of Furosemide.

REFERENCES

[1]. Patil, Jagadevappa. (2010). INCLUSION COMPLEX SYSTEM; A NOVEL TECHNIQUE TO IMPROVE THE SOLUBILITY AND BIOAVAILABILITY OF POORLY SOLUBLE DRUGS: A REVIEW.

[2]. Chaudhary VB: Cyclodextrin Inclusion Complex to Enhance Solubility of Poorly Water Soluble Drugs: A Review. Int J Pharm Sci Res.2013,4(1); 68-76.

[3]. Sareen, S., Mathew, G., & Joseph, L. (2012). Improvement in solubility of poor water-soluble drugs by solid dispersion. International journal of pharmaceutical investigation, 2(1), 12–17. https://doi.org/10.4103/2230-973X.96921.

[4]. Saravanakumar K,Shilpaja C, Bharathi T, Nagaveni P,Durga SRM (2022). Journal of Young Pharmacists, 14(2):192-197.

[5]. Loftsson T. (2017). Drug solubilization by complexation. International journal of pharmaceutics, 531(1), 276–280. https://doi.org/10.1016/j.ijpharm.2017.08.087.

[6]. Mohammed Jafar*, Fatima Ibrahim Alshaer, Fatima Ali Adrees(2018). "Cyclodextrin Ternary InclusionComplexation: A Strategy to Improve Solubility of Poorly Soluble Drugs", International Journal of Pharmaceutical and PhytopharmacologicalResearch, 8(6), pp.8-17.

[7]. TM.Khan, R.Patel,AH. Siddiqui. Furosemide. [Updated 2021 Mar 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499921/.

[8]. KD Tripathi, Diuretics, JAYPEE BROTHERS medical publishers (p) ltd, 2019, 1(8):625.

[9]. Jassim, Zainab. (2017). Formulation and evaluation of furosemide liquisolid compact. International Journal of Applied Pharmaceutics. 9. 39. 10.22159/ijap.2017v9i6.21458.

[10]. PhalleSupriya, Patel SG, Dhobale SM.Estimation of Frusemide in bulk and tabletformulation by UV spectrophotometric Areaunder Curve method, Int. Res. Journal of Science &Engineering, January 2018; Special Issue A3 : 96 - 100.

[11]. Garnero, C., Chattah, A. K., &Longhi, M. (2014). Improving furosemide polymorphs properties through supramolecular complexes of β-cyclodextrin. Journal of pharmaceutical and biomedical analysis, 95, 139–145. https://doi.org/10.1016/j.jpba.2014.02.017

[12]. Amrutha JV. Cotton Cellulose, Pre and Post Compression Studies of Tablets. InorgChemInd J. 2016;11(4):101.

[13]. Bhowmick, Mithun. (2017). PREFORMULATION, PRCOMPRESSION AND POST COMPRESSION EVALUATION OF BILAYER TABLET OF ASPIRIN AS IMMEDIATE RELEASE AND NICOTINIC ACID AS SUSTAINED RELEASE. NRI Institute of Pharmaceutical Sciences, Bhopal, Madhya Pradesh, India. 7. 55-70.

[14]. Iqubal, Mohammad Kashif. (2018). RECENT ADVANCES IN DIRECT COMPRESSION TECHNIQUE FOR PHARMACEUTICAL TABLET FORMULATION.

[15]. Ahad A, Bin Jardan YA, Raish M, Al-Mohizea AM, Al-Jenoobi FI. Hydroxypropyl-β-Cyclodextrin for Delivery of Sinapic Acid via Inclusion Complex Prepared by Solvent Evaporation Method. Processes. 2022; 10(10):2046. https://doi.org/10.3390/pr10102046.

[16]. Sapkal, N. P., Kilor, V. A., Shewale, B. D., Bhusari, K. P., &Daud, A. S. (2010). Study of the ComplexationBehaviour of Fexofenadine with β-Cyclodextrin. Indian journal of pharmaceutical sciences, 72(3),

318–323. https://doi.org/10.4103/0250-474X.70477.

[17]. Semcheddine, F., Guissi, N.elI., Liu, X., Wu, Z., & Wang, B. (2015). Effects of the Preparation Method on the Formation of True Nimodipine SBE-β-CD/HP-β-CD Inclusion Complexes and Their Dissolution Rates Enhancement. AAPS PharmSciTech, 16(3), 704–715. https://doi.org/10.1208/s12249-014-0257-x.

[18]. Ghosh A, Biswas S, Ghosh T. Preparation and Evaluation of Silymarin β-cyclodextrin Molecular Inclusion Complexes. J Young Pharm. 2011;3(3):205-210. doi:10.4103/0975-1483.83759.

[19]. Shirse, P., Rao, K.S., & Iqbal, M.M. (2012). FORMULATION AND EVALUATION OF CYCLODEXTRIN INCLUSION COMPLEX TABLETS OF WATER INSOLUBLE DRUG-GLIMIPIRIDE.

[20]. Voleti, Vijayakumar& Gladiola, B. &Madhusudhana, Cmm& RE, Ugandar. (2019). FORMULATION AND EVALUATION OF GASTRO RETENTIVE DRUG DELIVERY SYSTEM OF ZANAMIVIR USING DIFFERENT POLYMERS. Journal of Biomedical and Pharmaceutical Research. 8. 10.32553/jbpr.v8i4.641.

[21]. Sami, Ahmed. (2017). Formulation and Evaluation of Buspirone Oral Disintegrating Tablets Using Banana Powder. Journal of Global Pharma Technology.

[22]. Karkhile, Vishal &Sontakke, Manish &Barhate, Ritesh&Tupkari, S.V.. (2009). FORMULATION AND EVALUATION OF FLOATING TABLETS OF FUROSEMIDE. International Journal of Pharma Research and Development – Online. 1. 1-9.