Educational Administration: Theory and Practice
2024, 30(11), 2119-2125
ISSN: 2148-2403
https://kuey.net/

Research Article

Design, Development and Evaluation of Anti-Inflammatory Drug Etodolac by Crystallo-Co-Agglomeration Technique

Ritesh R. Popat[1*], Praveen Sharma[2]

[1*]Research Scholar, Department of Pharmaceutics, Oriental University, Indore (M.P.)
[2]Faculty of Pharmacy, Oriental University, Indore (M. P.)

Citation: Ritesh R. Popat, et al. (2024). Design, Development and Evaluation of Anti-Inflammatory Drug Etodolac by Crystallo-Co-Agglomeration Technique, *Educational Administration: Theory and Practice*, 30(7), 2119-2125
Doi: 10.53555/kuey.v30i11.10296

ARTICLE INFO

ABSTRACT

Etodolac is used to assist alleviate the symptoms of rheumatoid arthritis, osteoarthritis, and mild to moderate discomfort. However, these medications' bioavailability and absorption in the body are problematic. The design and assessment of crystal co-agglomerates made with different poloxamer concentrations are the focus of the current investigation. The study's goal was to improve the drug's solubility and pharmacological properties while also increasing its absorption in the body to improve therapeutic response. When the parameters of the manufactured Crystalo-Co-Agglomerates were assessed, it was discovered that the 5% batch was ideal due to its superior flow ability, highest drug content, and enhanced dissolution properties. It was shown that the creation of crystal co-agglomerates was an effective method for enhancing the different characteristics that can lower the likelihood of drug metabolism and provide improved therapeutic response and stability.

Keywords: Etodolac, NSAID, Crystalo Co-agglomeration, Poloxamer.

Introduction

Crystallo-co-agglomeration (CCA) is an innovative technique developed with the intention to provide the drugs with good micromeritic and mechanical characteristics. The process of CCA involves crystallization followed by simultaneous agglomeration of the drug with the aid of a good solvent and/or a bridging liquid and a bad solvent. This process enables designing of spherical agglomerates containing low dose drugs which are poorly flowable and compressible. The CCA require less processing time and may reduce the manufacturing as well as processing time during compression. The crystallo-co-agglomeration technique may be utilized to improve the micromeritic properties of powder materials utilized in direct compression. The resultant tablets may show improved crushing, compression, disintegration and dissolution profile when compared with the tablet utilizing other conventional methods.[1-2]

General strategies adopted for obtaining agglomerates [3]

The methods for obtaining agglomerated crystals can be categorized on the basis of achieving super saturation. The selection of method mainly depends on the nature of the drug and excipients as well as the objective of the study. In general, drugs and excipients are dissolved separately in their respective solvents. Next, both are mixed in glass vessels with high-speed rotation (approximately 900 – 1000 rpm) to achieve uniformity. The mixture turns cloudy once the agglomerates are formed. Agglomerates are collected by filtering and kept for drying overnight at room temperature.

Stages of growth of Agglomeration[4-5]

The growth of agglomerates follows a sequence of zonal divisions.

A. Flocculation zone I- Pendular bridges are generated by the bridging liquid in the flocculation zone, which displaces the solvent from the surface of the particle. The free floccules become compact aggregates in the zero growth zone. The trapped liquid leaks out of the microscopic floccules and rises to the surface.

B. Zero growth zone- The rate-limiting stage in the production of tiny agglomerates in the zero growth zone is the squeeze out of the bridging liquid from the pores of the first floccules.

Copyright © 2024 by Author/s and Licensed by Kuey. This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

C. Fast growth zone- A substantial amount of bridging liquid has been squeezed out of the surface of the little agglomerates at that time, which is where the fast development zone can be seen. Large size particles are created during the coalescence process by the chance collision of a well-formed nucleus. Successful collision requires a small amount of extra surface moisture on the nucleus.
D. Constant size zone- The agglomeration's growth is halted in the constant size zone.
Attrition, fracture, and shatter cause agglomerates to shrink even slightly over time.

Process Variables[6-7]

Process variables such as speed of agitation, time of process contribute the formulation aspects of crystallo co agglomerates.

Agitation

Emulsification or dispersion is the primary purpose of agitation. Agitation had an impact on the agglomerates' size, shape, sphericity, and strength. Increased sphericity and decreased strength of the agglomerates may be the results of high speed agitation. Additionally, it was shown that when agitation speed increases, the amount of time the procedure takes and the amount of agglomeration decrease.

Time required for batch processing

Agglomeration is completed at the moment of agitation. Inadequate agitation results in insufficient mixing of the different constituents, which inhibits the formation of agglomerates. Additionally, this lessens the amount of organic solvents that vaporize from the reaction vessel, whereas excessive agitation leads to fine formation. In CCA, the agglomeration determination end point is crucial. It can be determined by evaluating the supernatant's purity, the amount of remaining organic solvent, and the achievement of the right agglomeration size.

Significance of Crystallo-Co-Agglomeration[8-11]

a. CCA is useful in making agglomerates of one, two, or more drugs, high dose or low dose, with or without excipient.
b. It is possible to directly compress those drugs, which were unless otherwise impossible to do so, with improved micromeritic, mechanical, compressibility, compactability properties possessed through this technique.
c. Drug uniformity of agglomerates is unique.
d. With the right choice of polymers, controlled release dosage forms are makeable. improved bioavailability and dissolving properties.
e. Agglomerates of simple excipients can be produced to manufacture placebo medications. (talc agglomerates)
f) Agglomerates may be created as MUPS in the form of an encapsulated dosage form.
g) The shear required for compression is less than that of granules.
h) The entire process can be controlled by a single person.
i) The requirement of time and space are less.
j) As the process contains only single step it is possible to carry out it in a closed system. This prevents external contamination. So it is easy to follow cGMP.

Pharmaceutical Applications of Crystallo-Co-Agglomeration Technique [12]

1. With the help of the crystallo co-agglomeration method, drugs with larger doses can be immediately compressed with excipients.
2. In order to provide prolonged release formulations with predictable dissolving patterns, low dosage medicines might be agglomerated with excipients.
3. The method can be used to enhance a variety of qualities: micromeritic properties (flow ability, pack ability, compressibility) mechanical strength of particles, for avoiding contamination due to dust generation, improving solubility and dissolution character of poorly soluble drugs.
4. Single, two, or more low dose medications, as well as big dose pharmaceuticals, can be agglomerated using the CCA process with or without excipients.
5. The resulting spherical agglomerates are immediately compressible tablet intermediates and/or capsules having improved micromeritic properties (flow ability, pack ability), mechanical properties (friability, crushing strength and tensile strength, etc), compressibility, and compatibility.
6. Controlled drug release can be achieved with the help of certain polymers used during the agglomeration process.
7. Drug content uniformity in agglomerates can be easily maintained by agitation.
8. The crystallized drug forms miniscular form, hence, may improve drug dissolution and bioavailability. Agglomerates of plain excipients/diluents can be prepared and used as a placebo therapy.
9. Simultaneously, agglomerates having different drug release profiles can be prepared. The intact agglomerates can be given in the form of encapsulated dosage form as MUPS.

10. When compared to other granulation technologies, the shear needed to agitate a liquid system is smaller than when mixing solids. The entire agglomeration procedure can be managed by a single person. Consequently, the need for labor is reduced in comparison to other granulation techniques.
11. The time and space requirements are less for CCA because of curtailment of various unit operations used in conventional granulation technologies.
12. It is a single step process, carried out in a closed system, preventing contamination, and dust generation, thus guarantying practice of GMP.

Material and Method

Etodolac (API) obtained as gift sample from Alkem Pharmaceutical and other excipients like Poloxymer 188, Choloform, Water, Ethanol and aceton are used analytical Grade and purchased from molychem munbai

Formulation of Crystallo-Co-Agglomerates:

A solution of Etodolac (2 g) in acetone (3 mL) was added to a solution of hydrophilic polymer (Poloxymer 188, 1%, 3% 5% *m/V*) in 100 mL distilled water. The mixture was stirred continuously using a mechanical stirrer (Remi Motors, India) at 500 rpm to obtain agglomerates. The bridging liquid (dichloromethane, 0.5 mL) was added drop wise. The agglomerates were separated by filtration using Whatman filter paper and dried for 24 h at room temperature.

Evaluation Parameters

Solubility Determination:

Solubility studies of Etodolac were done according to method described by Higuchi and Connors. An excess quantity of drug was taken in vials containing 10 ml of media. The vials were shaken in water bath (100 strokes per min) for 24 hr at room temperature. The solutions were then filtered using Whatman filter paper and the solubility of the drugs were analyzed spectrophotometrically after suitable dilutions. The solubility of the drug was determined in distilled water, pH 1.2 buffer solution.

Standard calibration curve of Etodolac:

Accurately weighed 10 mg of Etodolac was transferred into the calibrated volumetric flask and dissolved in 10ml mixture of Ethanol and water (70:30 v/v) to achieve a stock solution of 1000 µg/mL (Stock-I). Stock-I solution was suitably diluted with co-solvent system of Ethanol and water to achieve a solution of 100 µg/mL (Stock II)

Calibration curve was prepared by diluting the stock-II solution to achieve different calibration standards representing 2, 4, 6, 8, 10 µg/mL strength. Absorbance of each calibration standard was measured at pre-identified λmax 278 nm using fixed wavelength measurement mode.

Determination of Micromeritic Properties:

The various Micromeritic Properties like Bulk density, Tapped density, Carr's Compressibility index, Hausner's ratio, Hausner's ratio of pure drug prepared Crystallo-Co-Agglomerates are determined using standard procedures.

Fourier Transform Infrared Spectroscopy:

The FTIR spectrum of pure drug Etodolac was subjected to an FTIR study for confirmation of the drug. The spectra were recorded in the range of 4000-500 cm-1 by using FTIR (alpha II Bruker, Germany) spectrophotometer. The instrument and sample chamber were purged with dry air to remove atmospheric water vapour. A blank spectrum was run to subtract from the sample spectra.

Differential Scanning calorimetry:

The molecular state of the pure drug Etodolac was evaluated by performing a DSC analysis. The drug sample was loaded in flat bottomed standard aluminium crucibles and hermetically sealed by cold welding using a crucible sealing press at 0.2 MPa pressure before analysis. The thermograms were obtained by DSC instrument (METTLER TOLEDO, Switzerland) at a heating rate of 10° C /min from 30° C to 300° C in a nitrogen atmosphere. The enthalpy and temperature of the DSC system was calibrated using standard aluminium pan.

Scanning Electron Microscopy (SEM):

SEM was employed to examine the surface topography and morphology of prepared CCA.14 To enhance the conductivity, an ion sputtering device (JEOL, JFC-1100 E, Japan) was used for 5 min under reduced pressure (0.001 torr) to coat gold (200°A) on the samples, which were then subjected to SEM (JEOL, JSM-840A, Japan).

Powder X-ray diffraction spectroscopy (PXRD):

X-ray diffraction pattern of pure drug and Crystallo-co-Agglomerates of Etodolac were obtained using the X-ray diffractometer (BRUKER D8 ADVANCE, Germany) at 40 kV, 30 mA and a scanning rate of 0.02 /min at the diffraction angle 20 over the range of 10-80° using Cu (as anode) radiation of wavelength 1.5406 A

Drug loading

The drug loading efficiency of prepared Etodolac 5% Crystallo-Co-Agglomerates crystals was determined by dissolving 100 mg of crystals in 100 mL of ethanol, followed by measuring the absorbance of appropriately diluted solution spectrophotometrically (Pharma Spec UV-1700, UV-Vis spectrophotometer, Shimadzu) at 278 nm.

Solubility studies of Crystalo co aggloromate

A quantity of prepared Etodolac 5% Crystallo-Co-Agglomerates crystals (about 100 mg) was shaken with 10 mL of distilled water or a solution of sodium lauryl sulphate (SLS) (2%, *m*/*V*) in a shaking water bath (100 agitations per min) for 24 h at room temperature. The solution was then passed through a 0.45 mm. membrane filter and the amount of the drug dissolved was analyzed spectrophotometrically.

Results and Discussion

Solubility Determination:

Table 1: Solubility Determination of Celecoxib

Solvent	Solubility
Water	Practically insoluble
DMF	Soluble
Ethanol	Soluble
DMSO	Soluble
Acetone	Soluble

Standard calibration curve of Etodolac:

A series of standard containing concentration from 2 to 10 µg/ml of Etodolac were prepared and absorbance was measured at λmax 278 nm against reagent blank. All spectral absorbance measurement was on Shimadzu UV-visible spectrophotometer

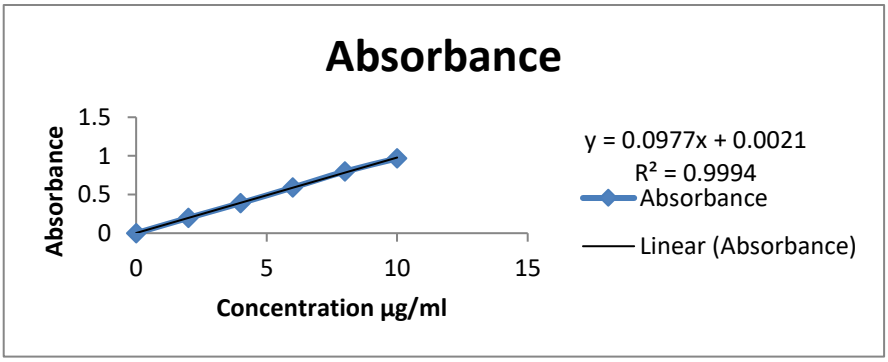

Figure 1 Calibration curve of Etodolac

Determination of Micromeritic Properties:

Micromeritic Properties	Etodolac Pure Drug	Etodolac Crystal-Co-Agglomerates
Bulk density	0.30 g/cm^3	0.66 g/cm^3
Tapped density	0.42 g/cm^3	0.76 g/cm^3
Carr's compressibility index	28.57	13.55
Hausner's ratio	1.4	1.15
Angle of repose	43.53^0	28.81^0

Fourier Transform Infrared Spectroscopy:

The potential intermolecular interaction of functional group on the surface of Etodolac were analysed by the FTIR spectra. The FTIR Spectra of Etodolc exhibited the characteristic peak observed at 3340 cm^{-1} corresponds to N-H stretching in amino groups. Additionally, peak observed at 3053 cm^{-1} corresponds to Aromatic Ring. The peak observed at 2932 cm^{-1} corresponds to C-H bond. The spectrum for Etodolac exhibited characteristic peaks at 1750 cm^{-1} corresponds to C=O stretch. The symmetrical stretch of the carboxyl group typically appears in the 1411 cm^{-1} region. 1266 cm^{-1} in an IR spectrum can indicate the

presence of a C-N stretch in aromatic amines. The peak around 1172 cm^{-1} often indicates a C-O stretching vibration in alcohols, carboxylic acids, esters, or ethers. The 788 cm^{-1} band can be associated with aromatic and alkali functional groups, specifically C=C.

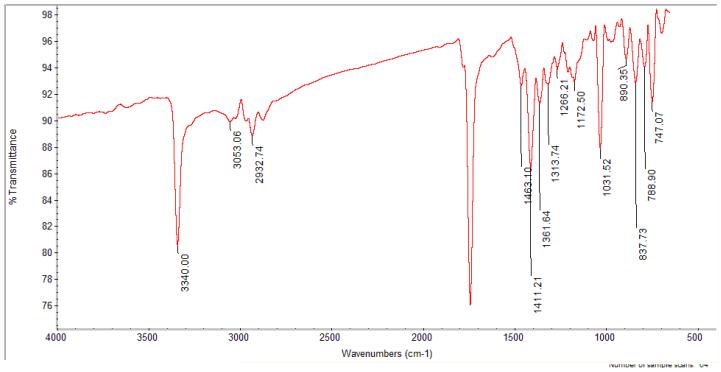

Figure 2 FTIR of Pure Drug Etodolac

Differential Scanning calorimetry:

The molecular state of the pure drug Etodolac was evaluated by performing a DSC analysis. The DSC curve provides qualitative and quantitative data about the physical state of material. From Fig no. 8.35, it evident that a sharp endothermic peak corresponds to Etodolac was observed near 151.93°C. It is as per reported value so the sample was authenticated.

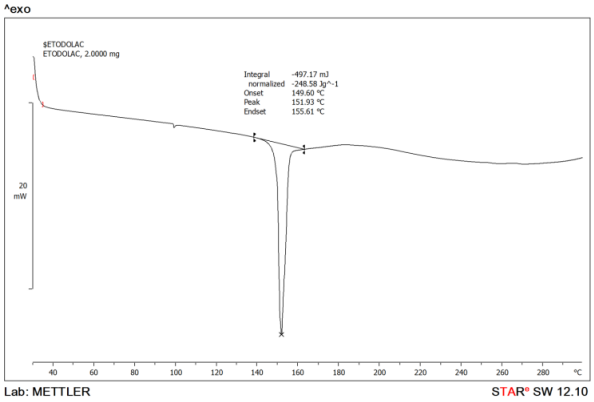

Figure 3 DSC of Pure Drug Etodolac

Scanning Electron Microscopy (SEM):

SEM was employed to examine the surface topography and morphology of Sample. The surface morphology and shape of Etodolac will be determined by using scanning electron. The Picture of Pure Etodolac drug shows irregular shape crystals with rough surface. With dimensions of 26.43 um in length and 16.45 um in width.

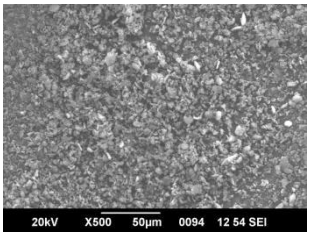

Figure 4 Sem of Pure Drug Etodolac at 500X

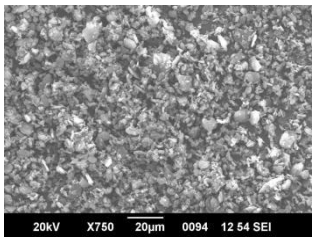

Figure 5 Sem of Pure Drug Etodolac at 750X

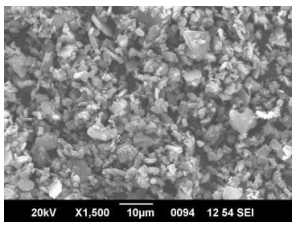

Figure 6 Sem of Pure Drug Etodolac at 1500X,

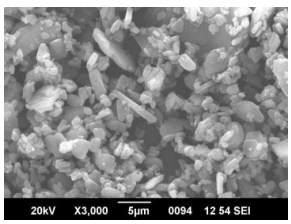

Figure 7 Sem of Pure Drug Etodolac at 3000X

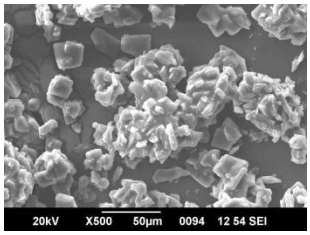

Figure 8 Sem of CCA of Etodolac at 500X

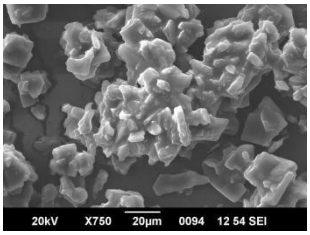

Figure 9 Sem of CCA of Etodolac at 750X

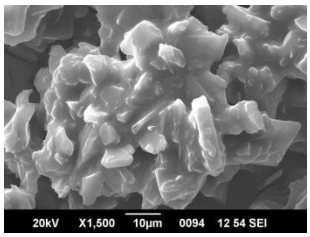

Figure 10 Sem of CCA of Etodolac at 1500X

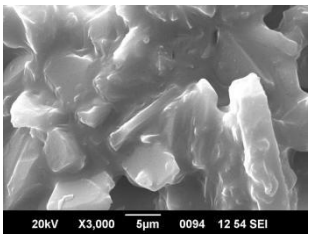

Figure 11 Sem of CCA of Etodolac at 3000 X

Powder X-ray diffraction spectroscopy (PXRD):

X-ray diffraction pattern of pure drug and Crystallo-co-Agglomerates of Etodolac were obtained using the X-ray diffractometer (BRUKER D8 ADVANCE, Germany) at 40 kV, 30 mA and a scanning rate of 0.02 /min at the diffraction angle 20 over the range of 10-80° using Cu (as anode) radiation of wavelength 1.5406 A. The Drug and formulation shows increase in peak size which indicated the formation Crystals.

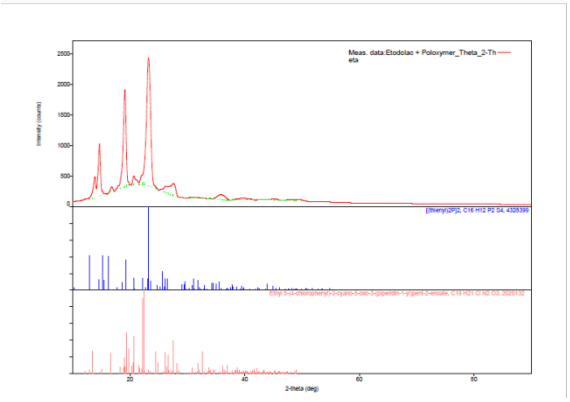

Figure 12 Etodolac+ poloxymer drug XRD Spectrum

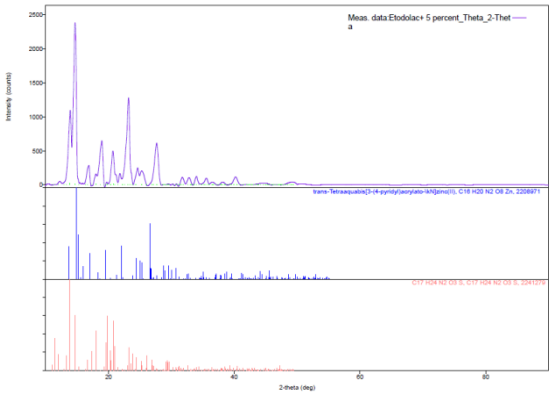

Figure 13 Etodolac Crystalo co aggloromate 5% XRD Spectrum

Drug loading

The drug loading efficiency of crystals was determined by dissolving Etodolac Crystalo co aggloromate 5%100 mg of crystals in 100 mL of methanol, followed by measuring the absorbance of appropriately diluted solution spectrophotometrically (PharmaSpec UV-1700, UV-Vis spectrophotometer, Shimadzu) at 278 nm.

Solubility studies of Crystalo co aggloromate

A quantity of Etodolac Crystalo co aggloromate 5% crystals (about 100 mg) was shaken with 10 mL of distilled water or a solution of sodium lauryl sulphate (SLS) (2%, *m*/*V*) in a shaking water bath (100

agitations per min) for 24 h at room temperature. The solution was then passed through a 0.45 mm. membrane filter and the amount of the drug dissolvedand the solubility was analysed and it was found to be completely soluble.

CONCLUSION

Etodolac's micromeritics and solubility were successfully improved using the Crystal-Co-Agglomerates production process, which will increase its bioavailability. This study suggests that the Crystal-Co-Agglomeration approach can improve Etodolac's micromeritics and solubility characteristics.

REFERENCES

1. Pawar AP, Paradkar AR, Kadam SS, Mahadik KR. Agglomeration of Ibuprofen with Talc By Novel Crystallo-Co-Agglomeration Technique. AAPS Pharm Sci Tech. 2004 ;5:30-35
2. Pawar AP, Paradkar AR, Kadam SS, Mahadik KR. Crystallo-Co-Agglomeration: A Novel Technique To Obtain Ibuprofen-Paracetamol Agglomerates. AAPS Pharm Sci Tech. 2004; 5 : 57-64
3. Bijaya Ghosh, Jayesh Patel, Preeta Bose and Digpati Roy. CRYSTALLO CO-AGGLOMERATION-A REVIEW. *International Journal of Recent Scientific Research* Research *2018;92(F),:24226-24230, February,*
4. V. R. Vemula, V. Lagishetty, and S. Lingala, Solubility enhancement techniques, Int Journal of Pharmaceutical Sciences Review and Research, 2001; 5(1): 41–51.
5. D. Sharma, M. Soni, S. Kumar, and G. D. Gupta, Solubility enhancement—eminent role in poorly soluble drugs, Res J Pharm and Tech, 2009; 2(2): 220–224.
6. Sarfaraz M D, Arshad Ahmed Khan K, Doddayya H, Reddy S R., Udupi R H. Particle Design of Aceclofenac-Disintegrant Agglomerates for Direct Compression by Crystallo Co Agglomeration Technique. AJPT, 2011; 11(2): 40-48.
7. P K Kulkarni, Mudit Dixit, Ashwini G Kini Akash Johri. Spherical agglomerates of mefenamic acid by solvent change method. IJPS, 2011; 2(2): 111-125.
8. Chandresh P P, Malay N Jivani and Bhupendra G P. Crystallo-co-agglomerations:The Novel Approach For Micro particulation. Res & Rev Health Care Open Acc J, 2018; 1(3): 65-70
9. Jolly CM, Lekshmi P, Constantine I, Bijin EN, Valsalakumari J, Pramod K. Crystallo-co-agglomeration: an innovative technique for size enlargement and improved flow properties of powders. J Mater Sci, 2013; 1: 1-14.
10. Lipinski, C.A. Drug-like properties and the causes of poor solubility and poor permeability. Journal of Pharmacological & Toxicological Methods, 2000; 44: 235-249.
11. V.B.Yadav, A V Yadav. Recrystallized agglomerates of indomethacin by emulsion solvent diffusion (ESD) technique. IJPBS, 2010; 1(1): 122-134
12. Parida R, Evaluation Parameters for Spherical Agglomerates Formed by Spherical Crystallization Technique. Int J Pharm Biol Sci, 2010; 1(3): 1-1