

**SOLID DISPERSION TECHNIQUE TO IMPROVE SOLUBILITY OF ACECLOFENAC****¹Sri Lahari Tanniru, ²Sai Jyoshna Mudavath, ³Ramya Ghanapuram and ⁴Hyma Ponnaganti**^{1,2,3}Department of pharmaceuticals, Sarojini Naidu Vanita Pharmacy Maha Vidhyalaya, Hyderabad, Telangana, India.⁴Associate Professor, Department of Pharmaceuticals, Sarojini Naidu Vanita Pharmacy Maha Vidyalaya, Hyderabad, Telangana, India.***Corresponding Author: Sri Lahari Tanniru**

Department of pharmaceuticals, Sarojini Naidu Vanita Pharmacy Maha Vidhyalaya, Hyderabad, Telangana, India.

Article Received on 22/10/2021

Article Revised on 11/11/2021

Article Accepted on 01/12/2021

ABSTRACT

Aceclofenac is confronted with challenge in conceiving appropriate formulation, due to low solubility and bioavailability. It is an analgesic and anti-inflammatory. aceclofenac is mainly used in treatment of ankylosing spondylitis, osteo arthritis, rheumatoid arthritis. To enhance the bioavailability of drug, Various compositions of aceclofenac solid dispersions were prepared by solvent evaporation method using mannitol and urea as carrier. The formulations evaluated for dissolution study and also characterized by FTIR study. Moreover, the study suggested the conversion of crystalline aceclofenac. And it shows no interaction between carrier and drug. Among all the formulations optimized formulation shown higher drug release% compared to other formulations. As compared to the pure drug, In vitro release rate of aceclofenac solid dispersion showed significant improvement.

KEYWORDS: Anti-inflammatory, bioavailability, osteoarthritis, crystalline, solid dispersion, dissolution, ankylosing spondylitis.**1. INTRODUCTION**

One of the major challenges in pharmaceutical research is to successfully develop solid dosage forms of drugs having poor solubility. Such poorly soluble drugs are usually classified as the biopharmaceutical classification system class II drugs with high permeability.^[4] To maintain correlation between drug absorption and corresponding clinical response considerable progress has been made in the solubility enhancement by different strategies in delivery of BCS class II drugs, but still its challenging to maintain the correlation. Solid dispersion is one of the effective techniques in pharmaceutical formulations to increase the biopharmaceutical characteristics of poorly water-soluble drugs.^[6,3] Solid dispersion is defined as the dispersion of drug in a matrix at solid state that has been used to improve the solubility of drugs. The drugs solubility enhancement can be endorsed to reduction in particle size, decrease in agglomeration, modification in the physical state of the drug from crystalline to amorphous, better wettability and even in proper dispersion of the drug on a molecular level.^[1] In solid dispersion drug was highly dispersed in the suitable carrier, which shows its most important feature.^[5] the techniques include melting method, spray dried dispersion, solvent evaporation method and other methods. Solid dispersion could increase the surface of the drug particles, which results in enhancing the drug release based on Noyes-Whitney equation. various approaches including physical, chemical and other modification have been attempted to improve the

bioavailability and solubility of the drugs. Among them, solid dispersion is promising technology to improve dissolution.^[10,12] Solvent evaporation is the simplest process for the preparation of solid dispersion where drug and appropriate polymers are triturated using a small volume of ethanol. The characteristic of solid dispersion depends upon the drug and carrier ratio, type of interaction, process used, type of carrier, degree of interaction between drug and carrier, composition of solvent, process conditions such as temperature, rate of cooling, temperature, humidity.^[11]

Methods of preparation of amorphous solid dispersion Fusion-method, Ball-milling, Solvent-evaporation, Hotmelt-extrusion, Lyophilization technique, Supercritical fluid methods.

Solvent evaporation method

To produce amorphous solid dispersion, solvent evaporation method is the easiest way, where the drug and carrier is solubilized in a volatile solvent. The first step involves the preparation of solution containing both drug and matrix material. The 2nd step in the method involves the removal of solvent by evaporation resulting in formation of a solid dispersion. To get optimal dissolution properties, mixing at molecular level is preferred. Using the solvent evaporation method, the pharmaceutical engineer faces two challenges. The first one is to mix both drug and matrix in one solution, which is difficult when they differ significantly in polarity. The

drug and matrix have to be dispersed in the solvent as fine as possible, to reduce the drug particle size in the solid dispersion. The second challenge is to prevent phase separation, in the solvent evaporation method. e.g., crystallization of either matrix or drug, during removal of the solvent.

Aceclofenac is an orally effective NSAID of phenyl acetic acid group, which possesses anti-inflammatory, analgesic properties.^[10] Among the NSAIDs (Non-steroidal anti-inflammatory drugs) it is well tolerated, with a lower incidence of gastrointestinal adverse effects. Because of its low aqueous solubility, it shows poor bioavailability and poor dissolution.^[14] It is an example of biopharmaceutical classification system class II compound and its oral bioavailability is determined by dissolution rate in the gastrointestinal tract. The improvement of aceclofenac dissolution rate is an issue

for enhancing its therapeutic efficacy and bioavailability.^[11]

2. MATERIALS AND METHOD

2.1 Materials

aceclofenac was procured from heterochemicals. Mannitol, urea and all other chemicals were procured from SD chemicals.

2.2 Methods

2.2.1 Preparation of solid dispersion

Solvent evaporation method
Solvent evaporation method was used for preparation of solid dispersion of aceclofenac. The composition is shown in table 1. In solvent evaporation method the drug and carrier's mannitol, urea along with methanol were triturated in 1:2, 1:3, 1:4, 4:1 ratio in mortar and pestle. Trituration was continued until the solvent gets evaporated.^[10]

Table 1: composition of solid dispersion formulations.

Formulation code	composition	Ratio
F1	Aceclofenac: mannitol	1:2
F2	Aceclofenac: mannitol	1:4
F3	Aceclofenac: mannitol	1:3
F4	Aceclofenac: mannitol	4:1
F5	Aceclofenac: urea	1:2
F6	Aceclofenac: urea	1:4
F7	Aceclofenac: urea	1:3
F8	Aceclofenac: urea	4:1

2.2.2 Optimization of solid dispersion

It is unavoidable to investigate the dissolution behavior, in order to evaluate the feasibility of solid dispersion technique. Hence, the appropriate dissolution medium is critical. Ultraviolet-visible spectroscopy method was developed to analyze the dissolution study. It was carried out with dissolution apparatus using the paddle method. Solid dispersion was placed into 900ml of dissolution medium at 37°C and paddle rotation speed at 100 rpm. At a predetermined interval (10, 20, 30, 40, 50, 60) 10ml of sample was withdrawn and equal volume of warmed fresh media was added. The concentration of aceclofenac was analyzed by an ultraviolet spectrophotometer at a wavelength of 275 nm.

2.2.3 Characterization of solid dispersion

Fourier-transform infrared spectroscopy
FTIR spectra were recorded at ambient temperature using a spectrum 100 spectrometer equipped with a pressure clamp and an attenuated total reflection accessory with a ZnSe crystal at wavelength of 4000-400 cm⁻¹. Samples of approximately 2mg were placed on the crystal with a calibrated lever and scans were collected.

Powder x-ray diffraction¹

PXRD studies were performed to identify the presence of crystalline or amorphous forms in aceclofenac powder, solid dispersion. PXRD patterns were obtained at room temperature using an x-ray diffractometer operated at 40KV, 30 mA current, using a scan speed 2 deg/min and scan range of 10-80 deg.

2.3 Evaluation of solid dispersion

Solid dispersion of aceclofenac was evaluated for micromeritic properties such as angle of repose, tapped density, carr's index, hausners ratio.

2.3.1 Angle of repose

Funnel method was most often used to determine the angle of repose of solid dispersion. Adjust the height of the funnel, in such a way tip of the funnel must touch the apex of the heap of dispersion. Accurately weighed quantity of dispersion was allowed to flow through the funnel on to the surface. The diameter of heap was measured and from that angle of repose was calculated by using the equation,

$$\tan \theta = h/r$$

where h= height of the cone, r= radius of the cone, θ = angle of repose.

2.3.2 Bulk density

Both loose bulk density and tapped density were determined. 2grams of solid dispersion of formulation was slightly shaken to break the formed agglomerates and introduced into the measuring cylinder. Initial volume was observed, cylinder was allowed to fall onto the hard surface from the height of 2.5cm, the tapping was continued until the volume shows no change. TBD was calculated by using the following equation,
 $TBD = \frac{\text{weight of powder taken}}{\text{tapped volume of packing}}$
 $LBD = \frac{\text{weight of powder}}{\text{volume of packing}}$

2.3.3 Compressibility index

The granules compressibility was determined by carr's compressibility index by using following formula.
 Carr's compressibility index% = $[(TBD-LBD) \times 100] / TBD$.

2.3.4 Hausners ratio

Hausners ratio of the formulation can be calculated by using the formula
 $\text{Hausners ratio} = TBD/LBD$
 Compressibility index has been defined by hausners.

2.4 Preparation of solid dispersion tablet

Among 8 formulations F4 was taken as the optimized formulation as the f4 shows good release and solubility properties. Required quantity of microcrystalline cellulose (MCC) and talc were added as a diluent and lubricant respectively to dried solid dispersion of optimized formulation. And then pulverised using motor and pestle. Mixture was passed through 50-mesh sieve. Magnesium stearate of required quantity was added as an anti-adherent and mixed well. The prepared dispersion was compressed into tablet using stationary rotary tablet press. Among 8 formulations F4 was taken as the optimized formulation.

Table 2: ingredients in preparation of solid dispersion tablet.

S.no	Ingredients	Qnt/tablet (in mg)
1	Solid dispersion	120
2	Croscarmellose sodium	15
3	Sodium saccharin	5
4	Micro crystalline cellulose	245
5	Lactose	100
6	Magnesium stearate	10
7	Talc	5
8	Total weight	500

Prepared tablets were evaluated for hardness, friability, weight variation, drug content, disintegration, invitro dissolution studies, wetting time, water absorption ratio.

2.5 Post formulation studies^[11]

2.5.1 Tablet thickness

10 tablets were randomly selected from formulation and thickness was measured individually by vernier calliper. average thickness was calculated and expressed in milli meter.

2.5.2 Hardness

The hardness of the tablets was determined by hardness tester (Monsanto tester) it was expressed in kilopascal(kp). Ten tablets were selected from the formulation and hardness of the tablets were determined and average was calculated.

2.5.3 Weight variation

Average weight was determined by selecting 10 tablets from the formulation. Then individual tablet weight was compared with that of average weight.

2.5.4 Friability

Roche friabilator was used to determine the friability of tablets. Utilizing a plastic chamber which revolves at a speed of 25rpm and drops the tablets to a distance of 6 inch in each revolution, tablets are subjected to combined effect of shock abrasion. A sample of pre-weighed

tablets was placed in Roche friabilator (friability tester) which was then operated for 100 revolutions for 4min. then the tablets were dedusted and reweighed. A loss of less than 1% in weight is generally accepted. Percent friability was calculated as.

$$W_{\text{initial}} - W_{\text{final}} / W_{\text{final}} \times 100.$$

2.5.5 Drug content

Tablet was taken and powdered accurately. Powder containing about 100mg of aceclofenac was taken and dissolved in 50ml of methanol in a 50ml volumetric flask, 0.1ml of this solution was taken and diluted upto 25ml with methanol and absorbance was noted at 275 nanometres.

2.5.6 Disintegration

The disintegration time of the tablet was determined using disintegration test apparatus. 900ml distilled water was used as disintegrating media at $37 \pm 0.2^\circ\text{C}$. time required for complete disintegration of all tablets were noted.

2.5.7 Wetting time

2 circular whatmann filter papers of 5cm diameter are placed in a Petri plate with a 5cm diameter. 6ml of water is added to the petriplate. A tablet is carefully placed on the surface of the Whatmann filter paper. Wetting would be noted as time taken for water to reach the surface of the tablet.

2.5.8 Water absorption ratio

Initial weight of the tablet was taken and the final weight was after the water absorption by the tablet. It is calculated by,

$$W = \frac{W_{\text{final}} - W_{\text{initial}}}{W_{\text{initial}}} \times 100$$

2.6 Invitro dissolution study

Invitro dissolution apparatus was rotated at 100 rpm. Phosphate buffer PH 6.8(900ml) was taken as dissolution medium. Temperature of the dissolution medium was maintained at 37 degrees Celsius. Aliquots(5ml) of

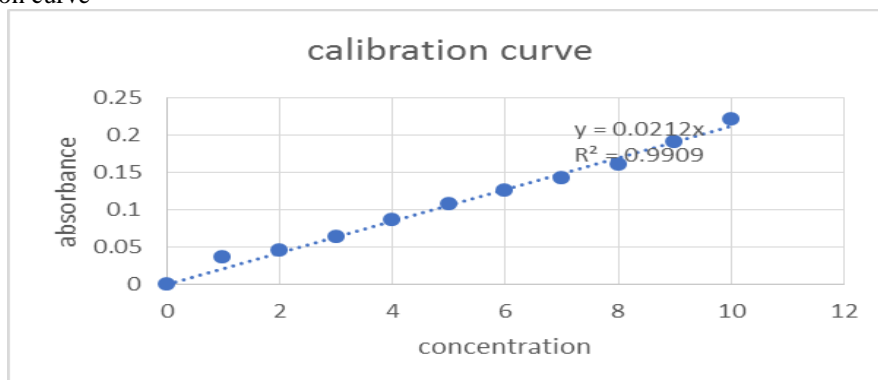
dissolution medium were withdrawn at specific time interval and filtered. Absorbance of filter solution was determined by uv- spectrophotometer at 275 nm and drug concentration was determined from standard calibration curve.

3. RESULTS AND DISCUSSION

Uv absorbance studies

Eight different concentrations of aceclofenac were absorbed under uv visible spectrophotometer. The standard graph was plotted using the absorbance results.

Standard calibration curve



Invitro drug release studies of optimized solid dispersion^[13]

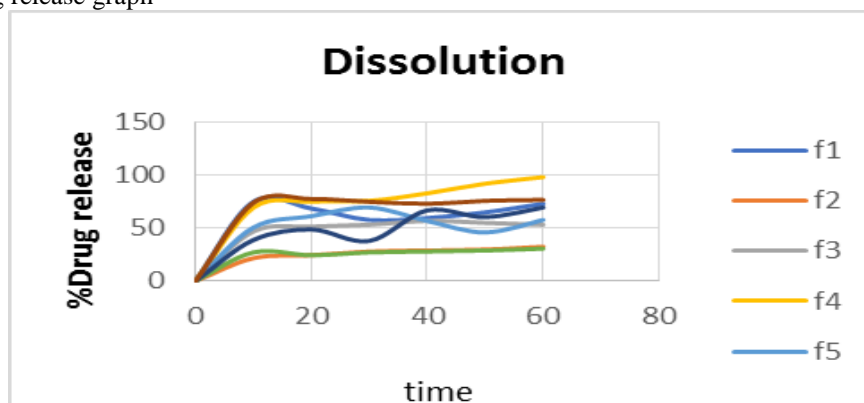
Dissolution behavior is a significant mean to guide the development of new formulation and could be used as a disintegrating method in a formulation selection. According to related literature, the dissolution was carried out in buffer solution. Absorbance was measured by uv visible spectrophotometer at 275 nm. The results

were calculated from standard calibration curve ($y = 0.021$, $R^2 = 0.9975$), of aceclofenac and Cumulative percentage release of the drug was plotted against the time. based on the dissolution profile among all the formulations F4 showed the best release. In view of solvent quantity and ratio of carrier, solid dispersion of drug: polymer ratio of 4:1 was selected for further study.

Table 3: percentage of drug release.

time	f1	f2	f3	f4	f5	f6	f7	f8
0	0	0	0	0	0	0	0	0
10	74.7	21.6	46.8	69.3	50.4	27	38.7	73.8
20	68.4	24.3	51.3	74.8	61.2	24.3	48.6	77.4
30	57.6	27.9	53.1	75.6	69.3	27	37.8	74.7
40	59.4	28.8	56.7	82.7	56.7	27.9	66.6	72.9
50	64.8	29.7	54.9	91.8	45.9	28.8	60.3	75.6
60	72.9	32.4	53.1	97.9	57.6	30.6	69.3	76.5

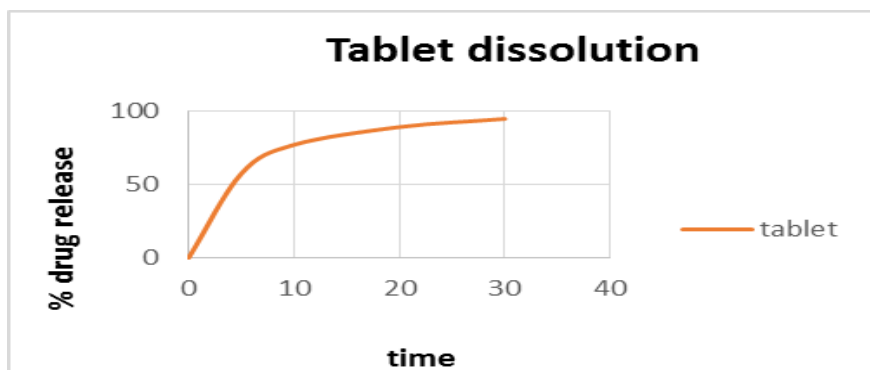
Percentage of drug release graph



Invitro drug release studies of solid dispersion tablet

Invitro drug release study of solid dispersion tablet was performed in the phosphate buffer for about 30 minutes.

Absorbance was measured using uv spectrophotometer. And graph was plotted cumulative drug release against time.

**Micromeritic properties of solid dispersion of aceclofenac**

Optimized Solid dispersion(f4) was found to be white without any color changes, free flowing and odorless

powder. Results of angle of repose, bulk and tapped density, compressibility index, hausners ratio are summarized in table 3.

Table 3: micromeritic properties of optimized solid dispersion.

formulation	Angle of repose	Bulk density	Tapped density	Carrs index	Hausners ratio
F4	22.5	0.457	0.534	14.42 ±0.02	1.20 ±0.02

Compatibility Study

Fourier transform infrared spectroscopy
Aceclofenac

FTIR spectrum of pure aceclofenac showed absorption bands such as O-H stretching at 3274.98cm^{-1} , aromatic ring stretch at 1448.55cm^{-1} , c=c stretching at 1698.84cm^{-1} , skeleton vibration of aromatic c-c stretching at 1541cm^{-1} , aromatic out plane bending for C-H at 750.31cm^{-1} these peaks were also shown by solid dispersion and optimized batch.

Mannitol

mannitol showed absorption bands at 3566.63 - OH stretching, C-O stretching were appeared at 1015.81cm^{-1} .

Sodium saccharin

Sodium saccharin showed absorption bands at 1586.21 , 1448.76 C-C benzene ring stretching, so_2 -N stretching at

1255.43 , negative saccharin ion with asymmetric absorption and carbonyl bending were appeared at 746.60 , 970.44 .

Aceclofenac solid dispersion

FTIR showed that the fundamental peak of aceclofenac solid dispersion at 3337.69cm^{-1} , 3236.65cm^{-1} , 2974.55cm^{-1} , 2359.70cm^{-1} , 1716.01cm^{-1} attributable to various functional groups like amines, aliphatic amines, secondary amines, alkenes, alkanes, alcohols, and phenols respectively.

Aceclofenac tablet powder

Tablet formulation shows peaks at 3841.09cm^{-1} , 2472.88cm^{-1} , 2116.36cm^{-1} , 974.06cm^{-1} , attributes to various groups like hydroxyl, moderate to prominent phenyl ring bands, ketone bands respectively.

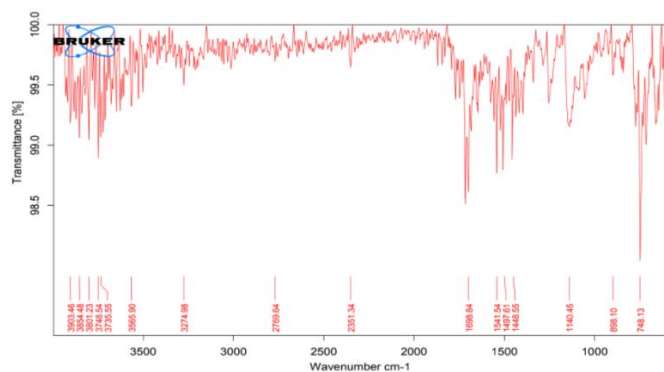


Figure 1: Ftir of aceclofenac

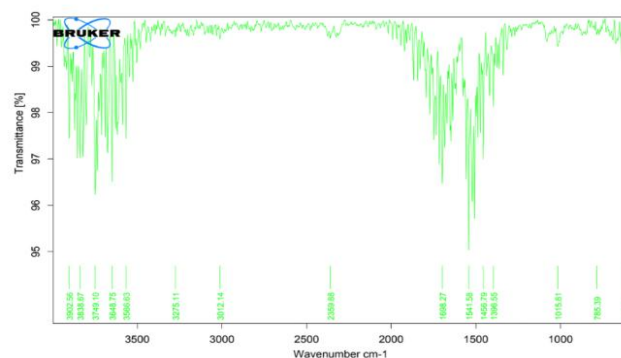
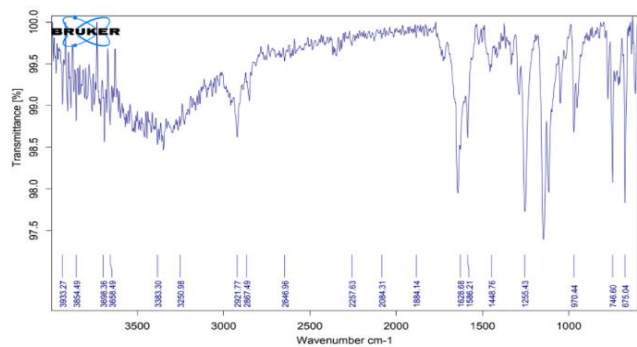


Figure 2: Ftir of mannitol



prepared using mannitol showed maximum hardness. Disintegration time of all the tablets was found to be less than 5 min. the friability of tablets of formulation were in the range of 0.622 i.e., less than 1%.

Drug release from solid dispersion was found to be higher as compared to plain aceclofenac. it could be suggested that in the solid dispersion, molecular dispersion of the drug in the polymeric carriers led to the improved dissolution rates by particle size reduction and surface area enhancement. Surrounding hydrophilic polymers shows an enhancement in drug solubility and bioavailability, dissolved extract from solid dispersion tablet formulation leads to higher absorption and higher oral bioavailability.^[2] Results also reveals that the solid dispersion prepared using mannitol gives higher dissolution rate as compared to that of solid dispersion prepared by using urea as a carrier.

The compatibility study using FTIR showed that the fundamental peak of aceclofenac retained with slight shifting, which reveals the aceclofenac is stable and retains its functional ability with mannitol.

CONCLUSION

The dissolution of aceclofenac was found to be more from solid dispersion prepared by using mannitol as a carrier. From various batches of solid dispersion of aceclofenac formulation f4 was selected as optimized formulation by considering dissolution, drug content, percent drug release. compatibility study using FTIR showed that, aceclofenac is compatible with mannitol and can be used for preparation of stable formulation. Hence study concluded that, solid dispersion of aceclofenac using mannitol can be prepared by solvent evaporation technique to enhance aqueous solubility, dissolution, and hence oral bioavailability.

REFERENCES

1. Samuel Solomon, et al., Insight into the ameliorating ability of mesoporous silica in modulating drug release in ternary amorphous solid dispersion prepared by hot melt extrusion, *European journal of pharmaceuticals and biopharmaceutics*, 2021 August; 165: 244-258.
2. Suputra Bunlung, et al., Development of raft-forming liquid and chewable tablet formulations incorporating quercetin solid dispersions for treatment of gastric ulcers, *Saudi pharmaceutical journal*, 2021 august 9.
3. A. Schittny, et al., Mechanistic insights into effect of surfactants on oral bioavailability of amorphous solid dispersion, *Journal of controlled release*, 2020 april; 165: 214-225.
4. Shimul Halder, et al., Impact of drying on dissolution behavior of carvedilol-loaded sustained release solid dispersion: development and characterization, *heliyon*, 2020 september 1.
5. Dong et al, Wenxiang et al., Preparation, characterization, and in vivo/vitro evaluation of polymer-assisting formulation of atorvastatin calcium based on solid dispersion technique, *Asian journal of pharmaceutical sciences*, 2018 November; 13: 546-554.
6. Niraj S. Trasi, et al., Physical stability and release and properties of lumefantrine amorphous solid dispersion granules prepared by a simple solvent evaporation approach, *International Journal of Pharmaceutics*, 2020 December, vol 2.
7. Arno A. Enose, et al., Formulation and characterization of solid dispersion prepared by hot melt mixing: a fast-screening approach for polymer selection, *Journal of pharmaceutics*, 2014 March.
8. Aejaz A, et.al., Formulation and invitro evaluation of aceclofenac solid dispersion incorporated gels, *International journal of applied pharmaceutics*, 2010; 2.
9. Naseeb Basha Shaik, et.al., Solubility Enhancement of Aceclofenac by Solid Dispersion, *Am. J. Pharm Tech Res*, 2018; 32-84.
10. M.V. Naga Bhushanam, et.al., Formulation studies on solid dispersion of celecoxib in super disintegrants alone and with pvp, *Rasayan j. chem*, 2009; 2: 691-698.
11. Nitave Sachin Anna Saheb, et.al., Formulation and Evaluation of Solid Dispersion Tablet of *Andrographis paniculate* Extract, *Pharmacognosy Journal*, 2018; 10: 1047-1054.
12. K. Arun prasad, et.al., Preparation and evaluation of solid dispersion of Terbinafine Hydrochloride Department of Pharmaceutics, 2010 August.
13. Samsuddin, et al., Development and evaluation of solid dispersion of spironolactone using fusion method, *International journal of pharmaceutical investigation*, 2016 August; 6(1): 63-68.
14. Shahinaze, et al., Preparation of solid dispersion systems for enhanced dissolution of poorly water soluble diacerein: in-vitro evaluation, optimization and physiologically based pharmacokinetic modelling, *International journal of pharmaceutical sciences and research*, 2017.
15. Eetu valkama, et al., Production and stability of amorphous solid dispersions produced by a freeze-drying method from DMSO, *International journal of pharmaceutics*, 2021 september.
16. Yiru wang, et al., The combination of hydroxypropyl methyl cellulose acetate succinate and L- lysine into ternary amorphous solid dispersions of quercetin to enhance its dissolution, *Carbohydrate polymer technologies and applications*, 2021 december.
17. Durgesh k. Jha, et al., Effect of Hypromellose acetate succinate substituents on miscibility behaviour of spray dried amorphous solid dispersion: Flory Huggins parameter prediction and validation, *Carbohydrate polymer technologies and applications*, 2021 December.
18. Afroditi kapourani, et al., Drug crystal growth in ternary amorphous solid dispersions: effect of surfactants and polymeric matrix-carriers,

International journal of pharmaceutics, 2021
December; vol 3.

19. Stefanie dohrn, et al., Predicting process design spaces drying amorphous solid dispersions, International journal of pharmaceutics, 2021 December.
20. Kumar Vinod M, et al., Comparative evaluation of fast dissolving tablets of aceclofenac prepared by different techniques, Int.j.res.ayurveda pharm, 2016 May; 7(3).