FORMULATION AND DEVELOPMENT OF SOLID DISPERSION OF INDOMETHACIN DRUG USING MIXED SOLVENCY

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Abstract:

The aim of research work formulation and in vitro evaluation of solid dispersion, ecofriendly solid dispersion techniques involve incorporating a poorly water-soluble drug into aa water-soluble carrier matrix to enhance its dissolution rate and bioavailability of drug" Mixed solvency concept can solve the problem of toxicity of organic solvent in use a pharmaceutical formulation. Wecan avoid the use of a high concentration of a single solubilizer use in different Formulation like Solid dispersion , Solubility Enhancement method of poorly water soluble drug Mixed solvency concept use for formulation dispersion in use for types of water soluble carrier like PVP-K30, Sodium benzoate, PEG6000 and sodium citrate and different ratio 1:1,1:2,1:3,1:4,1:5,1:6,1:7,and 1:8 and code of preparation SDMSIM-1,SDMSIM-2, SDMSIM-3,SDMSIM-4,SDMSIM-5, SDMSIM-6 SDMSIM-7 and SDMSIM-8 formulation of solid dispersion and examined evaluation parameter of solid dispersion all preparation and It found preparation code SDMSIM- 5 best Result min concentration show so it can use for formulation other dosage form preparation.

Key words: Solid dispersion, Mixed solvency, Solubility Enhancement Method, Poorly Water-Soluble drug.
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INTRODUCTION[1-4]: The mixed solvency concept was proposed by Dr. R.K Maheshwari in 2009.All substances which exist in a liquid state at room temperature are known as solvents. No solvent is the universal solvent. Whatever the name of a solvent we take, it is a good solvent for some solutes and a bad solvent for other solutes.

The mixed solvency concept proposed by Dr. R.K. Maheshwari states that and everything present in this Universe has got solubilizing power whether it is gas, liquid, or solid. All substances are known as solubilizers. Each substance (solubilizer) is a good solubilizer for some solutes and a bad solubilizer for other solutes. The name mixed solvency concept illustrates that a concentrated solution containing small concentrations of different solubilizers may give additive solvent actions or decreased solvent actions or synergistic solvent actions.

A concentrated solution may be made by using a combination of several solubilizers in safe concentrations. If this solution increases the solubility of insoluble drugs sufficiently then this technique may solve the problem of toxicity issue in pharmaceutical formulations any poor solvent for a particular solute may be made a strong solvent by the use of proper solubilizers. the mixed solvency concept may reduce the total concentration of individual solubilizers necessary to produce a modest increase in solubility by employing additives in lower concentrations from the point of view of the safety of solubilizers. This approach shall be applicable to prepare different dosage forms of the poorly soluble drugs.

MATERIAL AND METHOD:

Drug procurement : Indomethacin Procured from Pellets Pharma Limited Hyderabad, Sodium benzoate, Sodium acetate form S.D. fine chemicals, Mumbai.

Determination of Melting Point of Drug [5-8]: drug melting point was reported 155-160 ^{0}C and melting point was found 157^{0}C by capillary method.

Preparation of standard curve : calibration dilution was fallow the Beer-Lambert law in the concentration range of is suitable dilution for the estimation of indomethacin from methanol solutions.

Preparation calibration curve in methanol : Stock solution Concentration range of 5-25 µg/ml and were analysed spectrophotometrically at320 nm against a blank prepared in the same manner. The absorb ance data for different concentrations were subjected to regression analysis and found state line show.

Table 1: Preparation Standard calibration data of Indomethacin in Methanol at320nm

Sr.no	Concentration in µg /ml	Absorbance
1	0	0
2	5	0.131
3	10	0.264
4	15	0.396
5	20	0.524
6	25	0.656

Mean± SD(n=3)

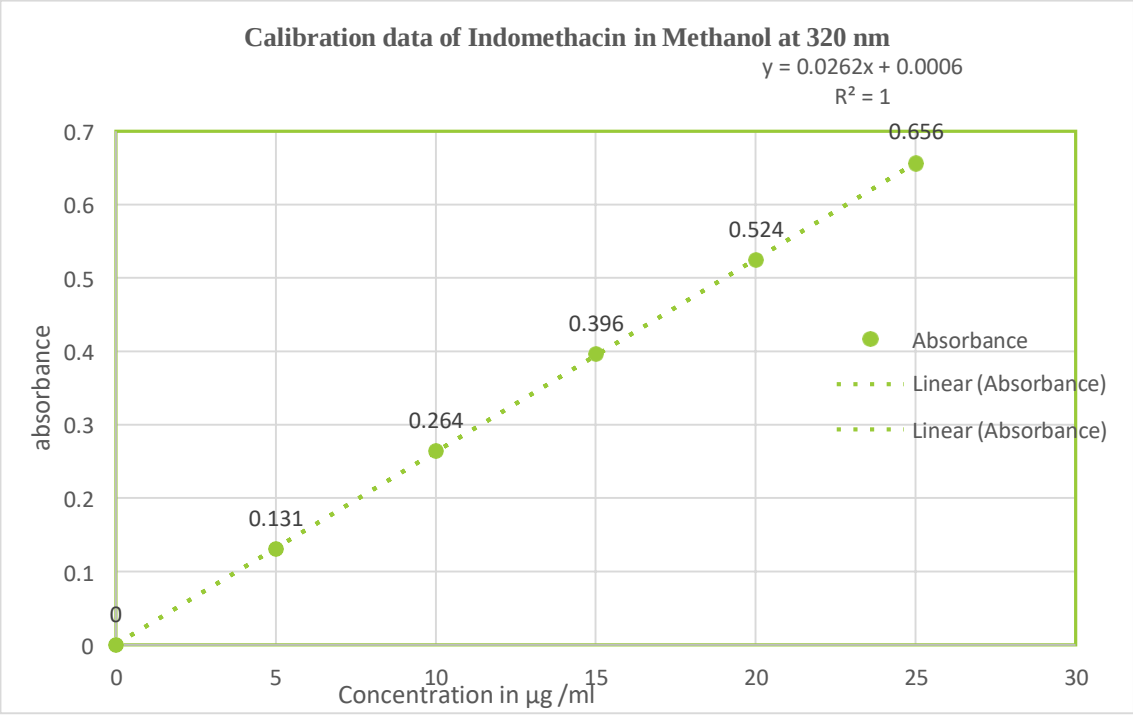

Figure 1: Standard calibration curve of Indomethacinin Methanol at 320nm

Identification of drug by FTIR [9-16]: Identification of drug Universal Attenuated Total Reflectance (UATR)ATR is a popular sampling technique for FTIR analysis, especially for solid or liquid samples. A sample is brought into contact with an ATR crystal (often made of diamond, germanium, or zinc selenide) which allows infrared light to penetrate a short distance into the sample. The light that is reflected back is analysed to obtain the spectrum. Identification of Drug was Examined by FTIR sample

drug standard O-H starching observed peak 3417.66 ,C-H starching 2970-2860 observed peak 2833.43,C=O starching Peak 1640-1750 observed peak 1554.63,C-H bending peak 1480-1350 observed peak1402.FTIR assume that over drug was stable condition.

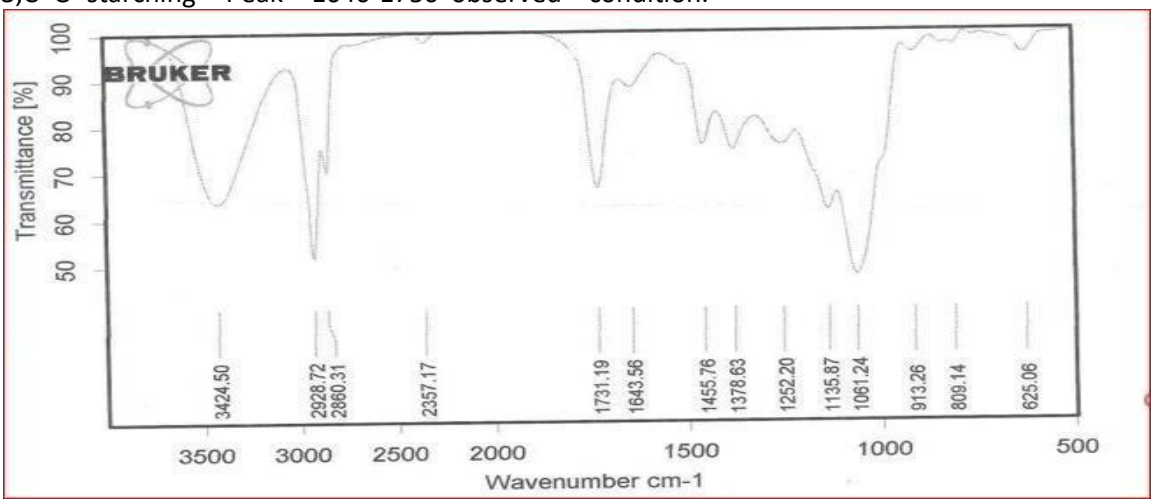

Figure 2: FTIR of indomethacin standard drug Reference

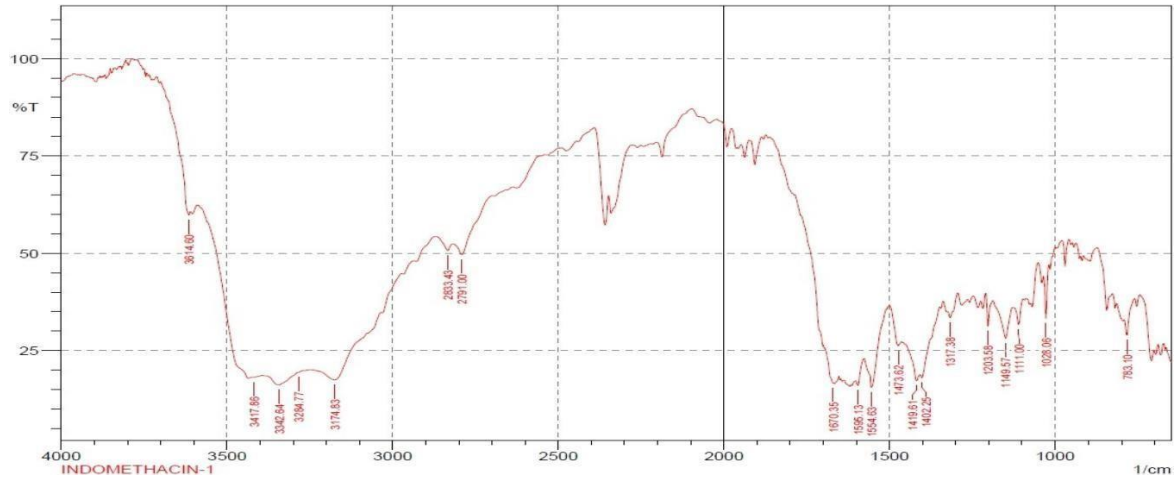

Figure 3: FTIR of indomethacin sample drug

Excipient Compatibility Study: done by FTIR UATR [17-21]

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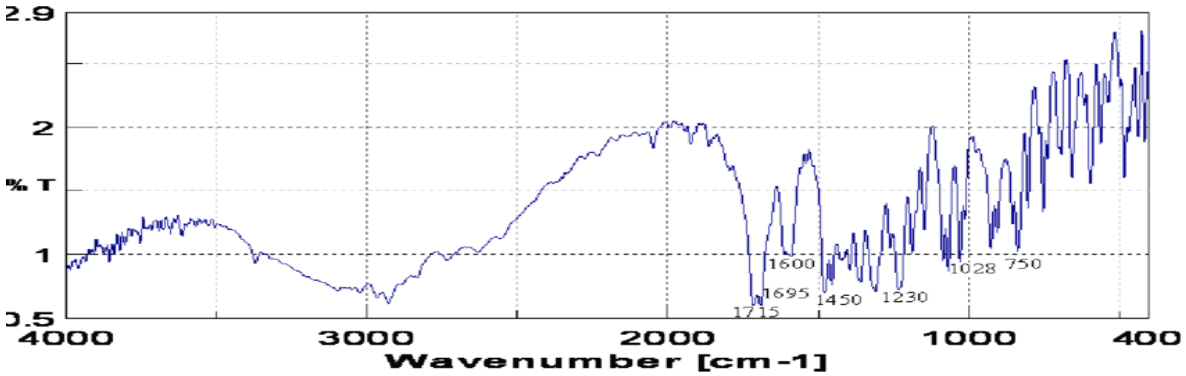

Figure 4: FTIR of indomethacin compability study

Solid dispersion: optimized formulation of solid dispersion(formulation code SDMSI-5 by mixed solvency concept use indomethacin drug

Procedure:

1. drug and carrier Ratio (1:5) Weigh 1.25 gm of PVP K 30, 1.25 gm of sodium benzoate, and 1.25 gm of PEG 6000 and 1.25 gm of sodium citrate. these additives are combined in a 1:5 ratio, aiming for a total mixture weight of 5 gm.

2. Mixing Place the accurately weighed PVP K 30, sodium benzoate, PEG 6000 and sodium citrate into a 100 ml beaker. Thoroughly mix these components to ensure a uniform distribution.

3. Adding Water Introduce the minimal warm, distilled water necessary to dissolve the mixture.

4. Dissolution: Utilize a Teflon-coated magnetic rice bead on a high-speed magnetic stirrer to aid the dissolution of the water-souble additives. This process ensures homogenous mixing and dissolution.

5. Drug Incorporation: Following complete solubilizer dissolution, add 1 gm of drug to the solution. Maintain the solution temperature between 55-60ºC to assist water evaporation.

6.Water Evaporation: As the solution evaporates, the magnetic rice bead's speed decreases due to reduced liquid content. Stirring stops once most water evaporates, indicating the formation of a wet solid dispersion

7.Drying: Spread the wet dispersion on glass petri plates and place them in a hot air oven set at 50±2ºC. This step facilitates further moisture evaporation, yielding a constant weight without additional loss.

8.Crushing and Sieving: After complete drying, carefully crush the solid dispersion using a glass pestle and mortar. Pass the crushed material through a mesh size 40 sieve, ensuring uniform particle size.

9. Storage: Store the processed solid dispersion in an airtight glass container. This safeguards the material from moisture and external contaminants, preserving its quality

Table 2: Composition of solid dispersion

IM-	carrier		Quantity taken (gm)			
		Indomethacin	PVPK30	Sodium Benzoate	Sodium citrate	EG4000
IM-1	1:1	1.00	0.25	0.25	0.25	0.25
IM2	1:2	1.00	0.50	0.50	0.50	0.50
IM-3	1:3	1.00	0.75	0.75	0.75	0.75
IM-4	1:4	1.00	1.0	1.0	1.0	1.0
IM-5	1:5	1.00	1.25	1.25	1.25	1.25
IM-6	1:6	1.00	1.50	1.50	1.50	1.50
IM-7	1:7	1.00	1.75	1.75	1.75	1.75
IM-8	1:8	1.00	2.0	2.0	2.0	2.0

Evaluation of solid dispersion [22-31]:

1. Physical Appearance: All the batches of Indomethacin solid dispersions were evaluated for colour and appearance.

Table 3: Physical Appearance of solid dispersion

ulation code	**Physical appearance of solid dispersion**			
Formulation Code	Colour	Odour	Taste	State
SDMSIM-1	Whitetolightyellow	Odourless	Slightlybitter	Fine granules powder
SDMSIM-2	Whitetolightyellow	Odourless	Slightlybitter	Fine granules powder
SDMSIM-3	Whitetolightyellow	Odourless	Slightlybitter	Fine granules powder
SDMSIM-4	Whitetolightyellow	Odourless	Slightlybitter	Fine granules powder
SDMSIM-5	Whitetolightyellow	Odourless	Slightlybitter	Fine granules powder
SDMSIM-6	Whitetolightyellow	Odourless	Slightlybitter	Fine granules powder
SDMSIM-7	Whitetolightyellow	Odourless	Slightlybitter	Fine granules powder
SDMSIM-8	Whitetolightyellow	Odourless	Slightlybitter	Fine granules powder

2. Percent Practical Yield (PY): Percentage practical yield were calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation.

PY(%)=Practical Mass(SD)/Theoretical Mass(Drug+Carrier)]×100

%Drug content= [Mact/Melt solvents]×100

3. Drug Content: The Physical mixture and solid dispersion equivalent to 5 mg of model drug were taken and dissolved separately in 5ml of methanol. The solutions were filtered using 0.45mmembrane filter and were further diluted and assayed by UV spectrophotometer at 320nm. The actual drug content was calculated using by following equation.

Drug Content= ActualEtoricoxib content in weight quantity of solid dispersion x100 Theoretical amount of indomethacin solid dispersion

Table 4:%Practical yield and drug content

Formulation code	% Practical yield	Drug content
SDMSIM-1	96.16±0.13	96.53±0.25
SDMSIM-2	97.53±0.19	97.33±0.78
SDMSIM-3	98.33±0.78	98.44±0.23
SDMSIM-4	98.26±0.25	99.16±0.07
SDMSIM-5	99.47±0.65	99.72±0.98
SDMSIM-6	98.26±0.25	99.47±0.65
SDMSIM-7	99.53±0.65	98.26±0.25
SDMSIM-8	99.16±0.07	98.53±0.59

4. Solubility Study: The solubility of drug was done DM water solubility of drug was analysed .a define quantity of the drug was dissolved in each investigated solvent at room temperature. DM water in screw capped glass tubes and shake non constant water bath shaker for 24 hours at 25°C . The solutions were examined physically for the absence or presence of drug particles and also by Spectro-Phometrically for quantitative determination of drug solubility investigated was done.

Table 5:Examined Solubility enhancement Different concentration at room temperature.

S.N.	Solubilizers	Concentration (% w/v)	Solubility(% w/v)
0	DM water	-	0.0465±0.012
1	SB	20	7.523±0.007
2	SB	40	14.226±0.011
3	SA	20	0.057±0.008
4	SA	40	0.883±0.005
5	SC	20	0.532±0.014
6	SC	40	1.616±0.017
7	UR	20	3.404±0.016
8	UR	40	6.198±0.014
9	Polaxomer407	20	0.418±0.006
10	Polaxomer407	40	0.816±0.012
11	PVP-K30	20	3.532±0.014
12	PVP-K30	40	6.616±0.017
13	PEG4000	20	0.546±0.008
14	PEG4000	40	1.642±0.004
15	PEG6000	20	0.537±0.006
16	PEG6000	40	1.548±0.009

Mean± SD(n=3)

SB -Sodium benzoate, SC-Sodium citrate, SA-Sodium acetate,PEG-4000, Polyethylene glycol 4000,PVP K 30-Polyvinylpyrrolidon K-30

Table 6: Equilibrium solubility in different blend four water-soluble additives

S.NO.	Blend of solubilizer	Total con. (%w/v)	Ratio	Solubility(% w/v)	%Solubility EnhancementRatio
	SB+SC+PEG4000 +PVP-K30	40	10:10:10:10:10	8.057±0.012	173.261
	SB+SC+PEG 6000+PVP-K30	40	10:10:10:10:10	6.883±0.006	148.012
	SB+SC+PEG4000+ Polaxomer407	40	10:10:10:10:10	4.332±0.014	93.161
	SB+SC+PEG4000+ urea	40	10:10:10:10:10	3.616±0.016	77.763
	SB+SC+PEG 4000+PEG6000	40	10:10:10:10:10	5.418±0.001	116.516

In-Vitro Dissolution Study of solid dispersion: Dissolution studies were performed assuring sink condition according to the Paddle method (USP) using USP type-II (Electro lab) apparatus .Thedissolutionmediumwas900ml Phosphate buffer 7.2 pH, keptat37˚C± 0.5˚C.tablet was placed, the paddle was rotated at 100 rpm for 20 min. Samples of 5 ml were withdrawn at specified time intervals and analysed spectrophotometrically at 320 nm using Shimadzu-1700UV-visible spectroscopy the samples withdrawn were replaced by fresh buffer solution. Each preparation was tested in triplicate and then mean values were calculated.

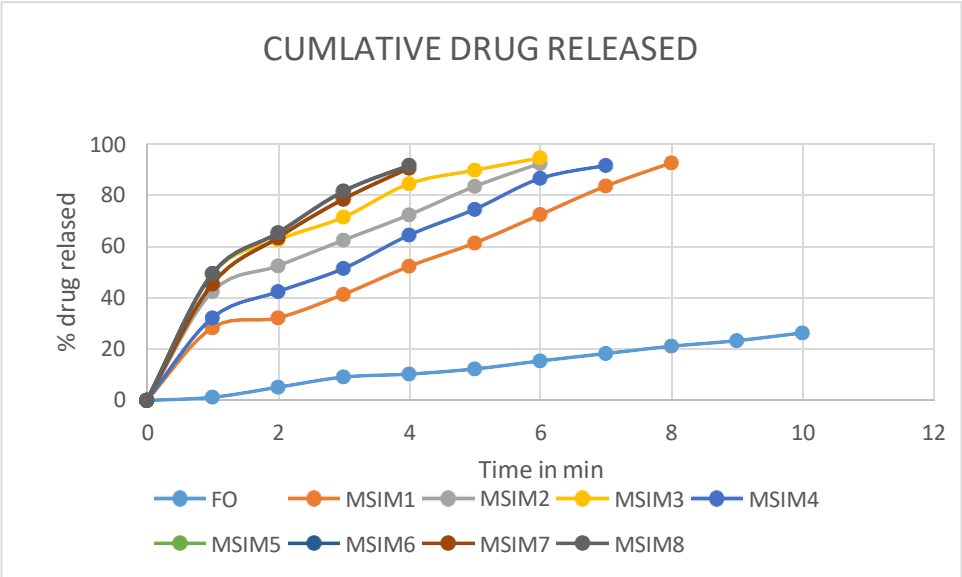

Figure 5: In-Vitro Dissolution Study of solid dispersion of indomethacin drug.

Stability Study : The stability of a tablet refers to its ability to maintain its physical, chemical, and therapeutic properties over time. It is an important characteristic that ensures the effectiveness, safety, and quality of the tablet throughout its shelf life and when consumed by the user. The stability of a tablet is influenced by various factors, including its formulation, packaging, storage conditions, and inherent chemical and physical properties all six batch formulation are stable physical and chemical as per guide line standard

Table 7: Storage condition as per ICH guide line

Study	Storage condition		Minimum time
	Temperature	Relative humidity (%)	
Long term	$25^0C \pm 2^0C$	60% ±5% RH	Long term
Intermediate	$30^0 \pm 2^0C$	65%± 5% RH	Intermediate
Accelerated	$40^0 \pm 2^0C$	75% ±5% RH	Accelerated

Result and Discussion: This research based solubility enhancement by mixed solubility method in this research work formulation in vitro evaluation of dispersible tablet using ecofriendly solid dispersion techniques mixed solvency concept use for formulation dispersion in use water soluble carrier like PVP-K30,Sodium benzoate, PEG 6000 and sodium citrate and different ratio 1:1,1:2,1:3,1:4,1:5,1:6,1:7,and 1:8 and formulation of 8 blend of mixed solvency code of formulation code of preparation SDMSIM-1,SDMSIM-2, SDMSIM-3,SDMSIM-4,SDMSIM-5, SDMSIM-6 SDMSIM-7 and SDMSIM-8 formulation of solid dispersion and examined evaluation parameter of solid dispersion all preparation and It found preparation code SDMSIM- 5 best Result show min concentration.

REFERENCE :

1. Mark Gibson et.al," Pharmaceutical Pre formulation and Formulation", Drugs and The Pharmaceutical Sciences, Informa Healthcare USA, Second Edition, Vol. 99, Page 18-50 ,2009
2. Larry L. Augsburger , Stephen W. Hoag "Pharmaceutical dosage forms tablets ,"

Informa healthcare USA,Third Edition ,Vol. 2, Page 465 -480 ,2008.

3. Lachman Leon, Herbert A.Lieberman,Josheph L.Kanig, "The Theory and Practice of Industrial Pharmacy", Varghese publishing house Bombay , Second Edition ,4th Reprint ., Page 171-195,1991.
4. Geoffrey D. Tovey ," Pharmaceutical Formulation the Science and Technology of Dosage Form", The Royal Society of Chemistry ,First Edition ,Page 1-19 ,2018.
5. George A. Menge, " a study of melting point determination" , public health and marine hospital service of united state USA, Page 25-30 ,1910.
6. Yihong qiu , Yisheng chen and Rao v. Mantri , "developing solid oral dosage forms Pharmaceutical Theory & Practice", Academic Press is an imprint of Elsevier London ,second edition ,Page 3-20 ,2017.
7. Geoffrey D. Tovey ," Pharmaceutical Formulation The Science and Technology of Dosage Form", The Royal Society of Chemistry ,first edition ,Page 1-5 ,2018.
8. N.K Jain , "Pharmaceutical Product Development ,"CBS Publisher &Distributer" , New Dehli, First Edition 2006, Page 61-85, 2006.
9. Brian C. Smith ,"Fundamental of Fourier transform infrared spectroscopy", CRC Press is an imprint of the Taylor & Francis Group, an Informa business ,Second edition ,Page 1-16 ,2011.
10. Janethan withrow "Infrared and Raman spectroscopy (concept and application) Academic Studio USA ,Page 13-21,2016.
11. Brian C. Smith ,"Fundamental of Fourier transform infrared spectroscopy", CRC Press is an imprint of the Taylor & Francis Group, an Informa business ,Second edition ,Page 90-94 ,2011.
12. Brian C. Smith ,"Fundamental of Fourier transform infrared spectroscopy", CRC Press is an imprint of the Taylor & Francis Group, an Informa business ,Second edition ,Page 129-114 ,2011.
13. Mark Gibson et.al," Pharmaceutical Pre formulation And Formulation", Drugs and The Pharmaceutical Sciences, Informa Healthcare USA, Second Edition, Vol. 99, Page 26-40 ,2009.
14. Sandeep Rathor, Chouhan M. and Omveer Singh , "Enhancement of Solubility And Dissolution Characteristics Of Etoricoxib By Solid Dispersion Technique Using Different Grade Of Peg Carrier Using." Journal of Pharmaceutical Negative Results ,Page 3233-3242.,2023 .
15. Yihong Qiu "Developing Solid Oral Dosage Forms Pharmaceutical Theory & Practice" Mica Haley USA ,Page 151-175, 2017.
16. Ali, Karima Fadhil, R. M. Albakaa, and Zinah Hussein Ali. "New assay method UV spectroscopy for determination of Indomethacin in pharmaceutical formulation." Journal of Chemical and Pharmaceutical Research ,Vol .7 Issue 4 , Page 1591-1596, 2015.
17. Rathod, Swati B., et al. "Method development and validation of indomethacin in bulk drug and capsule formulation by using mix hydrotrophy." Research Journal of Pharmaceutical Dosage Forms and Technology ,Vol .10 Issue 3 , Page 175-178,2018.
18. Newton JM, Razzo FN. Interaction of formulation factors and dissolution fluid and the in vitro release of drug from hard gelatin capsules. J Pharm Pharmacol ,vol. 27, Page 78,2009.
19. Fazil, Mohammad, Shahid Husain Ansari, and Javed Ali. "Development and evaluation of solid dispersion of spironolactone using fusion method." International journal of pharmaceutical investigation ,Vol. 6, Issue 1, Page 63,2016 .
20. Kaur, Jatinder, et al. "Improvement of drug solubility using solid dispersion." Int J Pharm Pharm Sci ,Vol. 4, Issue 2, Page 47-53. ,2012.
21. Pan, Ryh-Nan, Jing-Huey Chen, and Russel Rhei-Long Chen. "Enhancement of dissolution and bioavailability of piroxicam in solid dispersion systems." Drug development and industrial pharmacy ,Vol.26, Issue 9, Page 989-994.,2000.

22. Eloy, Josimar Oliveira, and Juliana Maldonado Marchetti. "Solid dispersions containing ursolic acid in Poloxamer 407 and PEG 6000: A comparative study of fusion and solvent methods." Powder technology ,Vol. 253, Page 98-106,2014.
23. Akiladevi, D., et al. "Preparation and evaluation of paracetamol by solid dispersion technique." Int J Pharm Pharm Sci ,Vol. 3, Issue 1, Page 188-191,2011.
24. Vyas, Jigar, Hemant Parmar, and Himan Patel. "Comparative Study of Etoricoxib Loaded Solid Dispersion and Beta-cyclodextrin Complexes for improvement of Dissolution Profile." Research Journal of Pharmaceutical Dosage Forms and Technology ,Vol. 12, Issue 2, Page 63-67,2020.
25. Eloy, Josimar Oliveira, and Juliana Maldonado Marchetti. "Solid dispersions containing ursolic acid in Poloxamer 407 and PEG 6000: A comparative study of fusion and solvent methods." Powder technology ,Vol. 253, Page 98-106, 2014.
26. El-Badry, Mahmoud, Gihan Fetih, and Mohamed Fathy. "Improvement of solubility and dissolution rate of indomethacin by solid dispersions in Gelucire 50/13 and PEG4000." Saudi Pharmaceutical Journal ,Vol. 17, Issue 3, Page 217-225,2009.
27. Mesnukul, A., K. Yodkhum, and T. Phaechamud. "Solid dispersion matrix tablet comprising indomethacin-PEG-HPMC fabricated with fusion and mold technique." Indian Journal of Pharmaceutical Sciences ,Vol. 71, Issue 4, Page 413-415,2009.
28. Mark Gibson et.al," Pharmaceutical Pre formulation And Formulation", Drugs and The Pharmaceutical Sciences, Informa Healthcare USA, Second Edition, Vol. 99, Page 368-390 , 2009.
29. Larry L. Augsburger , Stephen W. Hoag "Pharmaceutical dosage forms tablets ," Informa healthcare USA,third edition ,Vol. 2, Page 465 -480 ,2008.
30. Lachman leon,Herbert A.Lieberman,Josheph L.Kanig, "The Theory and Practice of Industrial Pharmacy", Varghese publishing house Bombay , Second edition ,4th repreint ., Page 171-195,1991.
31. Geoffrey D. Tovey ," Pharmaceutical Formulation The Science and Technology of Dosage Form", The Royal Society of Chemistry ,first edition ,Page 1-19 ,2018.