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A MIXED SOLVENCY APPROACH TO IMPROVED FORMULATION DEVELOPMENT AND CHARACTERIZATION OF A RAPID-RELEASE NON-STEROIDAL ANTI-INFLAMMATORY DRUG

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ABSTRACT

The formulation development and characterization of rapid-release non-steroidal anti-inflammatory drugs (NSAIDs) via a mixed solvency approach represent a significant advancement in pharmaceutical science. This study investigates the utilization of mixed solvency concepts to enhance the solubility and dissolution rates of NSAIDs, thereby facilitating their rapid release. Through systematic optimization of formulation parameters, including solvent selection, co-solvency ratios, and surfactant concentrations, novel NSAID formulations with improved drug delivery profiles were developed. The characterized formulations were subjected to rigorous physicochemical analyses and in vitro dissolution studies to evaluate their performance. The results underscore the efficacy of the mixed solvency approach in achieving enhanced formulation development and rapid-release characteristics for NSAID drugs. By leveraging the synergistic effects of multiple solvents and surfactants, this approach offers a versatile and efficient strategy for overcoming drug solubility challenges and enhancing therapeutic efficacy. This research contributes to the advancement of pharmaceutical formulation science and holds promise for improving the efficacy and patient compliance of NSAID medications.

INTRODUCTION

A class of pharmaceuticals known as non-steroidal anti-inflammatory drugs (NSAIDs) is frequently prescribed to treat fever, inflammation, and pain.Among them, indomethacin stands out as a potent NSAID with a broad spectrum of therapeutic applications, including the management of rheumatoid arthritis, osteoarthritis, and acute gouty arthritis.[1] However, despite its efficacy, the clinical utility of indomethacin is often limited by its poor aqueous solubility and slow dissolution rate, leading to delayed onset of action and erratic absorption kinetics. Consequently, there is a pressing need to develop novel formulation strategies that can enhance the solubility and dissolution properties of indomethacin, thereby facilitating its rapid release and improving therapeutic outcomes.[2]

MIXED SOLVENCY APPROACH:

The mixed solvency approach or concept is an innovative approach in pharmaceutical formulation science aimed at improving the rates of solubility and dissolution of medications that are not very water soluble.Traditional solubilization techniques often rely on a single solvent or surfactant to improve drug solubility. However, the mixed solvency concept goes beyond this by utilizing a combination of solvents, co-solvents, and surfactants to create a more effective solubilizing environment.[3]

In mixed solvency, the selection of solvents and surfactants is based on their individual solubilizing properties as well as their synergistic effects when combined. By carefully choosing the components and optimizing their concentrations, mixed solvency formulations can overcome the limitations of traditional solubilization techniques and significantly enhance drug solubility.[4]

The underlying principle of mixed solvency lies in altering the intermolecular interactions within the drug-solvent system to promote drug dissolution. This may involve breaking down drug aggregates, disrupting crystal lattice structures, or increasing the

mobility of drug molecules within the solvent medium. As a result, mixed solvency formulations can lead to faster and more complete drug dissolution, ultimately improving drug bioavailability and therapeutic efficacy.[5]

Mixed solvency has been successfully applied to a wide range of poorly water-soluble drugs, including NSAIDs, antibiotics, antifungals, and anticancer agents. By offering a versatile and efficient approach to solubilization, mixed solvency has become an essential tool in pharmaceutical formulation development, particularly for drugs with challenging solubility profiles.[6]

DRUG AND POLYMER PROFILE:

Analgesic, anti-inflammatory, and antipyretic qualities make indomethacin a popular non-steroidal anti-inflammatory medication (NSAID). 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3- is its chemical designation, and it is a member of the arylalkanoic acid class.as seen in Figure 1.[7]

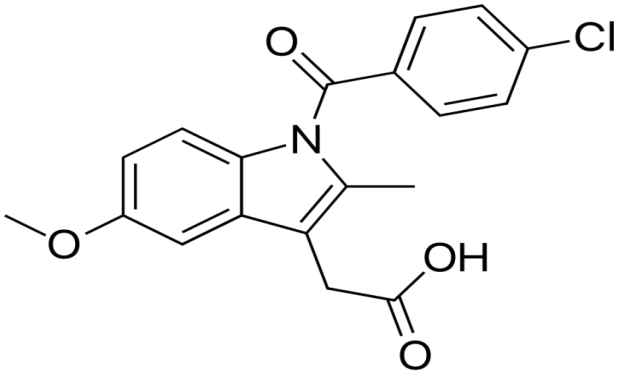


Figure 1: Chemical structure of indomethacin [8]

Indomethacin is frequently used to treat a variety of ailments, including tendonitis, bursitis, gout, and arthritis, by reducing pain, swelling, and inflammation.

Table 1: profile of indomethacin [9-11]

Molecularformula	$C_{19}H_{16}ClNO_4$
IUPACname	1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1-H-indole-3-aceticacid
Molecularweight	357.79g.mol^{-1}
Description	Awhitetoyellow-tan,crystallinepowderhavingnot morethan aslightodour.
Melting point	155-162°C
LogP	Octanol/water3.655
pKa	4.5
UV max.absorbance	320 nm
Stability	Unstableinalkaline solution

Mechanism of Action:

By preventing the body from producing prostaglandins—chemicals that produce pain, inflammation, and heat—indomethacin works. Indomethacin inhibits COX nonselectively. It is a strong prostaglandin synthesis inhibitor that lowers the activity of neutrophils.The body normally contains prostaglandins, which are hormone-like molecules with a variety of functions, including pain, fever, and inflammation.[12]

Indications: It is prescribed for various conditions, including:[13]

Arthritis: Rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis are among the various forms of arthritis that are frequently treated with Indomethacin.

Gout: It can lessen the discomfort and swelling brought on by gout flare-ups.

Bursitis and Tendonitis:. Indomethacin is occasionally recommended to lessen inflammation in the tendons and bursae, which are fluid-filled sacs that cushion joints.

Fever: Although it is less prevalent, it can also be used to lower fever.

Dosage Forms: Indomethacin is available in various forms, including oral capsules, extended-release capsules, and suppositories for rectal administration.[14]

Dosage: The ailment being treated, the intensity of the symptoms and the patient's reaction to the drug all affect the dosage. To lower the risk of stomach discomfort, it is usually taken two to four times a day with food or milk. [15]

Side Effects: The following are typical indomethacin adverse effects: headache, nausea, vomiting, diarrhoea, drowsiness, dizziness, and elevated blood pressure. High dosages or prolonged use may raise the risk of severe side effects like bleeding or stomach ulcers. cardiovascular events such as heart attacks or strokes, as well as kidney issues.[16]

Precautions: Those with a history of kidney dysfunction, cardiovascular illness, gastrointestinal issues, pregnancy, or breastfeeding should use it with caution. It's critical to adhere to the recommended dosage and course of treatment to reduce the possibility of negative consequences. [17]

Interactions: Blood thinners, corticosteroids, selective serotonin reuptake inhibitors (SSRIs), other NSAIDs, and several blood pressure drugs are among the drugs that may interact with indomethacin. Always let your doctor know about all of your prescriptions. you're doing to steer clear of any encounters. [18]

Contraindications: Peptic ulcer illness, severe heart failure, recent heart bypass surgery, and NSAID hypersensitivity are among the conditions for which Indomethacin should not be used. [19]

SOLID DISPERSION:

Enhancing the solubility, dissolving rates, and bioavailability of insoluble or weakly soluble medications is known as solid dispersion. By melting the physical mixes of the medicines and water-soluble carriers, a solid dispersion was created. [20]

MATERIAL AND MEETHOD:

Selection of drug and excipients:

Indomethacin is selected as model drug and Sodium benzoate(SB), Niacinamide, PEG-PEG-6000(P6K) are used as carriers to prepare solid dispersion, Magnesium Stearate as lubricant, Aerosil as glidant .

Identification and preformulation study:

Melting point determination:

The melting point of indomethacin drug sample was determined using open capillary method.

UV Spectrophotometrically analysis of Indomethacin:

After being carefully weighed, 10 milligram's of Indomethacin were added to a 100 milliliter volumetric flask. After dissolving 10 ml of methanol to produce a stock solution with a concentration of 100 µg/ml, the volume was raised to 100 ml with demineralised (DM) water. This stock solution was produced using DM water, and the concentration was 20 µg/ml. A Shimadzu 1700 doubling beam UV/visible spectrophotometer was then used to scan the sample between 200 and 400 nm, using DM water as a blank. Figure 2 displays

Infrared study of Indomethacin drug sample:

Using a Shimadzu hydraulic press, indomethacin and KBr were compacted into a pellet.Using an FTIR spectrophotometer (Shimadzu 8400-S), the drug's infrared spectra was captured in the 400–4000 cm-1 wave number range and displayed in Fig. 3.

Preparation of calibration curves:

50 mg of Indomethacin was accurately weighed and transferred to 50 ml volumetric flask. 20 ml of methanol was added to the dissolve the drug & then volume was made up to 50 ml with methanol so as to obtain a solution of 1 mg/ml. 2ml of the above solution was diluted with 0.1 n hcl up to 100 ml to give 20 µg/ml stock solution. appropriate dilutions of the stock solution were made with 0.1 N HCL inconcentration range of 4-20 µg/ml. the absorbances of the resulting drug solutions were recorded spectrophotometrically against 0.1 N HCL as blank. The data is recorded in table 3 and graphically represented in fig.4.

Preparation of solid dispersions of Indomethacin using mixed-solvency concept:

Organic solvents are used in solid dispersion technology that uses the mixed-solvency idea. The medication is insoluble in water, but the solubilizers (carrier) in this procedure are soluble in it. The medicine becomes soluble in water when there are a lot of solubilizers present. Next, water is eliminated using appropriate evaporation methods to obtain solid bulk (solid dispersion).

A solid dispersion was made in a 1:6 ratio using precisely weighed 2.625 g of niacin amide, 3 g of sodium benzoate, and 0.375 g of PEG-6000 in a 100 ml beaker. This mixture's total weight was 6 g. Then, the least quantity of heated Because less water will be used Demineralised water that was sufficient to dissolve the aforesaid mixture was added at a temperature of 70 to 80 °C. This gave the drug less time to evaporate and may not have a detrimental effect on its chemical stability (during water removal).. Teflon-coated magnetic rice beads were stirred on a high-speed magnetic stirrer to aid in the solubilising agents' dissolution. One gramme of indomethacin was dissolved in the aforementioned solution following the full dissolution of the solubilizers, and To help the water evaporate, the temperature was kept between 55 and 60 degrees Celsius. . The establishment of a wet solid dispersion was indicated by the rice bead's automatic decrease in speed as evaporation progressed and its cessation of stirring once the majority of the water had evaporated. The resulting wet solid dispersion was spread out on a petri dish and stored in a hot air dry oven set at 50+ 2ºC so that any remaining moisture could be readily evaporated and a constant weight could be achieved without any additional weight loss from evaporation. Following thorough drying, solid dispersions were mashed using a glass pestle and mortar, then sieved #60 before being placed in an airtight glass bottle to be used later.Table 5 shows that the composition of solid dispersions varies.

Characterization of solid dispersion:

Any technique for monitoring powder flow needs to be realistic, helpful, repeatable, sensitive, and produce results that are significant. Using a variety of standardized test techniques to describe the many facets of powder flow as required by the scientist in pharmaceuticals. The solid dispersions' micrometric characteristics were examined as follows:[21]

- Bulk density
- Tapped density
- Hausner ratio
- Compressibility index
- Angle of repose

Dissolution rate studies:

Using U.S.P. (type II) dissolving test equipment with paddle rotation at 75 rpm, the solid dispersion or physical mixture equal to 20 mg of Indomethacin was examined in dissolution rate tests. Two media were used for the dissolution tests: 900 ml of 0.1 N HCl (pH 1.2) and Phosphate buffer at pH 7.2. A constant temperature of 37 +/- 0.5°C was maintained. Afterward, 10 milliliters of the sample were taken out and subjected to spectrophotometrically analysis for drug content. Add new dissolving media to replace the sample that was taken out. Determine the dosage and the dissolution study findings, which are displayed in Table 8 and Figure 5.

Formulation of tablets:

Tablets are prepared only for selected solid dispersions which have shown high solubility and better drug release. Tablets of selected solid dispersions were prepared by direct compression method,containing a quantity equivalent to 20 mg of drug using avicel ph-112, magnesium stearate, aerosol (table 2).

AvicelPH-112,&aerosil were blended thoroughly and then solid dispersion quantity equivalent to 20 mg of drug was incorporated & finally magnesium stearate was added as lubricant. Die cavity of tablet machine was set for 200 mg and then tablet was compressed.

Table 2: Composition of fast release tablet of indomethacin

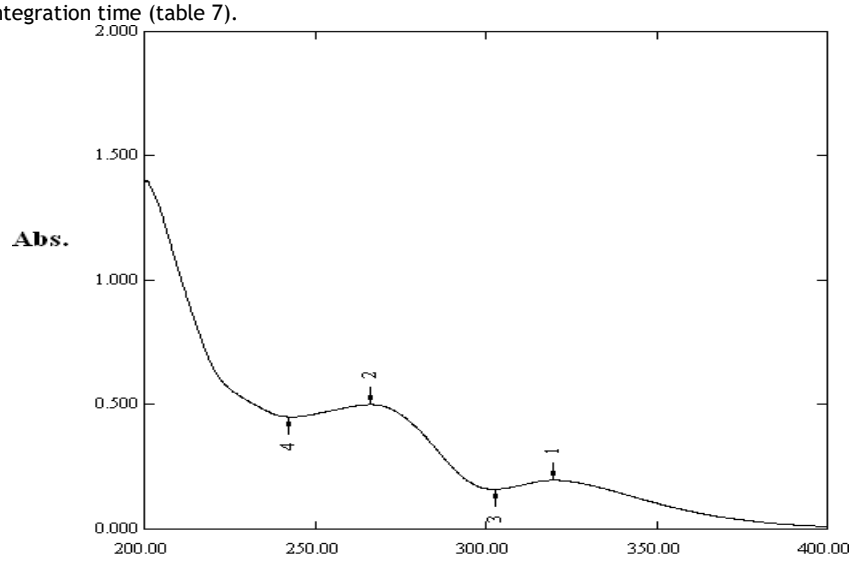
S. No.	Ingredient	Quantity(mg)
1.	Soliddispersion (1:6)	140
2.	AvicelPH-112	55
3.	Magnesiumstearate	3
4.	Aerosil	2

Evaluation of prepared tablets:

All prepared tablets were evaluated as hardness, friability, weight variation, Dissolution study, Disintegration time (table 7).

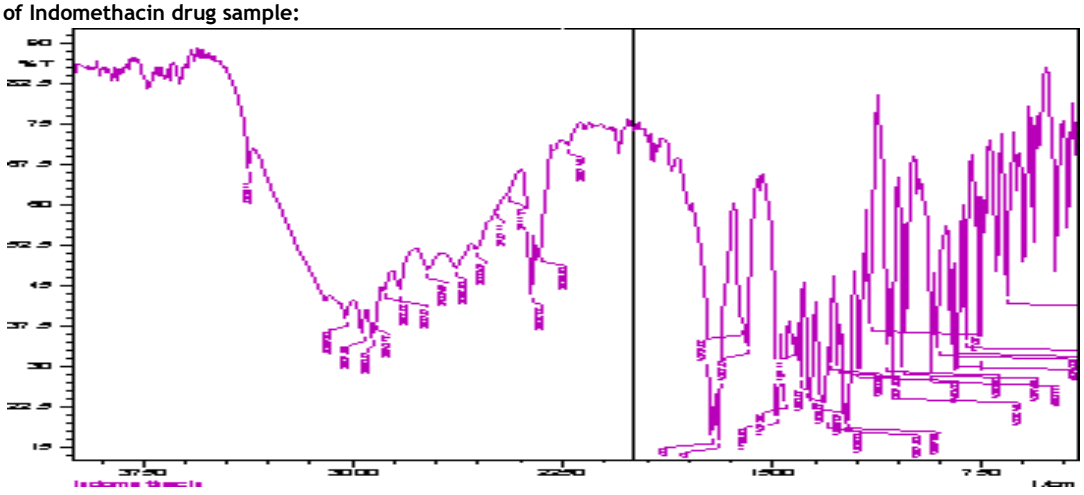
RESULTAND DISCUSSION:

UV Spectrophotometric analysis:



Result: The drug sample exhibited .

Infrared study of Indomethacin drug sample:



Preparation of calibration curve:

Table 3: Absorbance data of calibration curve of Indomethacin

Concentration (µg/ml)	Absorbance			
	Set1	Set2	Set3	Average
0	0	0	0	0
4	0.065	0.065	0.071	0.067
8	0.132	0.136	0.137	0.135
12	0.209	0.208	0.204	0.207
16	0.271	0.274	0.274	0.273
20	0.337	0.342	0.341	0.340

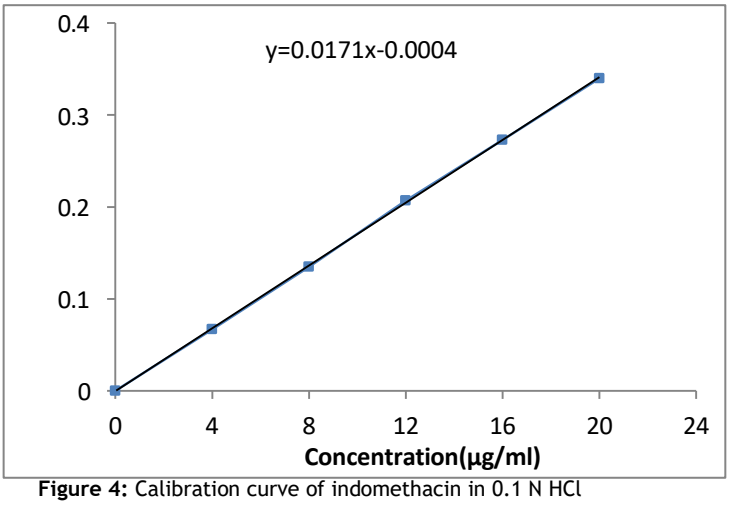


Figure 4: Calibration curve of indomethacin in 0.1 N HCl

Solubility studies in blends containing different solubilizers:

Table 4: Solubility of Indomethacin in solutions of individual solubilizers

S. No.	Solubilizer	Averagesolubility			Solubility enhancement ratio*
		20% (w/v)	30% (w/v)	40% (w/v)	
1	Sodium Acetate	0.014	0.021	0.034	3.148
2	Sodium Benzoate	0.409	1.890	3.562	329.907
3	Sodium Citrate	0.017	0.019	0.028	2.685
4	Urea	0.137	0.152	0.247	22.870
5	Niacinamide	0.234	0.437	0.583	54.074
6	PEG-4000	0.023	0.025	0.056	5.185
7	PEG-6000	0.022	0.036	0.073	6.851

*insolutions containing40%w/vsolubilizer

Result: From the results of above table 4 it was concluded that solubility of indomethacin increased with the rise in concentrations of solubilizer. Highest solubility was obtained in 40% w/v sodium benzoate solution.

Preparation of solid dispersions of Indomethacin using mixed-solvency concept:

Table 5: Different Composition of solid dispersions

S.No.	Drug:solubilizer blend ratio	Quantitytook (gm)			
		Indomethacin	PEG - 6000	Sodium benzoate	Niacinamide
1	1:6	1.00	0.375	3.00	2.625
2	1:8	1.00	0.500	4.00	3.500
3	1:10	1.00	0.725	5.00	4.275
4	1:12	1.00	0.950	6.00	5.050

Characterization of solid dispersion:

Table 6: Results of micromeritic properties of solid dispersions

S.No.	Parameter	Result	Inference

1	BulkDensity(gm/cm^3)	0.534	-
2	Tapped Density(gm/cm^3)	0.656	-
3	CompressibilityIndex	20.0	Fair
4	HausnerRatio	1.246	Fair
5	Angleofrepose	32°	Good

Result: The values of bulk density and tapped density show the free flowing property of solid dispersions (table 6). The values of compressibility index, angle of repose and Hausner ratio shows that the flow character of solid dispersion is fair.

EVALUATION OF TABLET:

Evaluation of Indomethacin tablet:

Table 7: various evaluationof Indomethacin tablets

S.No	**Parameter**	**Results**
1.	Weight Variation	**pass**
2.	Hardness	4.0 ± 0.14
3.	%Friability	0.27%
4.	Disintegrationtime	2 min.

Dissolution study of tablets:

Table 8: Dissolution of formulated tablets

S.No.	**Time(hr)**	**% CumulativeDrugrelease**
1	10	21.30
2	20	32.34
3	30	53.44
4	40	75.45
5	50	78.46
6	60	89.65
7	120	90.11

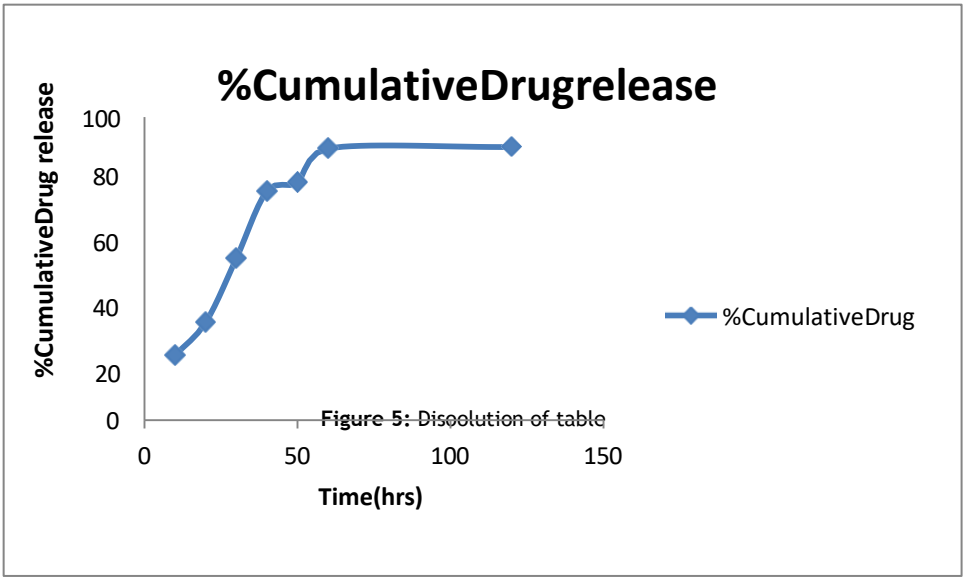


Figure 5: Disoolution of table

Stability studies (30 days):

Table 9: Evaluation data of tablets after one month

S.No	**Parameter**	**Results**
1.	GeneralAppearance	Smooth circular disc, elegant.
2.	Weight Variation	pass
3.	Hardness	3.80 ± 0.15
4.	%Friability	0.36 %
5.	Disintegrationtime	2 min.

Stability study of formulations at one month duration revelealed that there are minute change in friability. Hardness, Weight variation has negligible changes (table 9).

CONCLUSION

In conclusion, the formulation development and characterization of a rapid-release indomethacin drug through the mixed solvency approach represent a significant advancement in pharmaceutical science. Through meticulous optimization of solvent composition, surfactant concentration, and drug-excipient ratios, this approach achieves enhanced solubility and dissolution rates of indomethacin, leading to rapid drug release from the dosage form.The successful application of the mixed solvency approach offers several key benefits, including improved therapeutic efficacy, faster onset of action, and enhanced patient compliance. By overcoming the challenges associated with the poor aqueous solubility of indomethacin, this formulation provides healthcare practitioners with a valuable therapeutic option for managing pain and inflammation associated with conditions such as arthritis and gout.

Furthermore, comprehensive characterization studies ensure the compatibility, stability, and integrity of the formulated product, paving the way for its successful translation from the laboratory to clinical practice. Overall, the formulation development and characterization of a rapid-release indomethacin drug through the mixed solvency approach hold immense promise for addressing unmet medical needs and improving patient outcomes in the treatment of inflammatory disorders.

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