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ENHANCED FORMULATION DEVELOPMENT AND CHARACTERIZATION OF RAPID-RELEASE NON-STEROIDAL ANTI-INFLAMMATORY DRUG THROUGH MIXED SOLVENCY APPROACH

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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.

Keywords: Formulation development, Rapid-release, Non-steroidal anti-inflammatory drugs (NSAIDs), Mixed solvency approach.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of medications widely used to alleviate pain, inflammation, and fever. 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 enhancing the solubility and dissolution rates of poorly water-soluble drugs. 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

Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) that is widely used for its analgesic, anti-inflammatory, and antipyretic properties. It belongs to the class of arylalkanoic acids and is chemically designated as 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid (figure 1).[7]

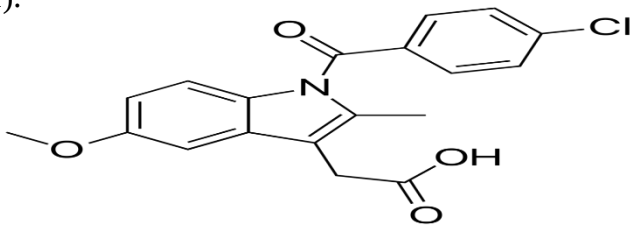


Figure 1: Chemical structure of indomethacin [8]

Indomethacin is commonly used to relieve pain, swelling, and inflammation caused by various conditions such as arthritis, gout, bursitis, and tendonitis. Table 1 indicating a profile of indomethacin;

Table 1: profile of indomethacin [9-11]

Molecular formula	$C_{19}H_{16}ClNO_4$
IUPAC name	1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1-H-indole-3-acetic acid
Molecular weight	357.79 $g.mol^{-1}$
Description	A white to yellow-tan, crystalline powder having not more than a slight odour.
Melting point	155-162 ˚C
LogP	Octanol/water 3.655
pKa	4.5
U V max. absorbance	320 nm
Stability	Unstable in alkaline solution

Mechanism of Action: Indomethacin works by inhibiting the production of prostaglandins, which are chemicals in the body that cause inflammation, pain, and fever. Indomethacin is nonselective COX inhibitor. It is a highly potent inhibitor of prostaglandin synthesis and suppresses neutrophil activity. Prostaglandins are hormone-like molecules normally found in the body, where they have a wide variety of effects, some of which lead to pain, fever, and inflammation.[12]

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

- **Arthritis:** Indomethacin is often used to treat different types of arthritis, including rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.
- **Gout:** It can help relieve the pain and inflammation associated with gout attacks.
- **Bursitis and Tendonitis:** Indomethacin is sometimes prescribed to reduce inflammation in the bursae (fluid-filled sacs that cushion joints) and tendons.
- **Fever:** It can also be used to reduce fever, although this is less common.

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

Dosage: The dosage varies depending on the condition being treated, the severity of symptoms, and the patient's response to the medication. It's typically taken 2 to 4 times daily with food or milk to reduce the risk of stomach upset. [15]

Side Effects: Common side effects of indomethacin include stomach upset, nausea, vomiting, diarrhea, headache, dizziness, drowsiness, and increased blood pressure. Long-term use or high doses may increase the risk of serious side effects such as gastrointestinal ulcers or bleeding, kidney problems, and cardiovascular events like heart attack or stroke. [16]

Precautions: It should be used with caution in individuals with a history of gastrointestinal disorders, cardiovascular disease, kidney dysfunction, or those who are pregnant or breastfeeding. It's important to follow the prescribed dosage and duration of treatment to minimize the risk of adverse effects. [17]

Interactions: Indomethacin may interact with other medications, including other NSAIDs, blood thinners, corticosteroids, selective serotonin reuptake inhibitors (SSRIs), and certain blood pressure medications. Always inform your healthcare provider about all the medications you are taking to avoid potential interactions. [18]

Contraindications: Indomethacin is contraindicated in individuals with a history of hypersensitivity to NSAIDs, peptic ulcer disease, severe heart failure, or recent heart bypass surgery.[19]

SOLID DISPERSION

Solid dispersion is define as the method of improve the solubility, dissolution rates and bioavailability of poorly soluble or insoluble drugs. The solid dispersion involved formation of admixture of drugs with water-soluble carriers by melting of their physical mixtures. [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 Spectrophotometric analysis of indomethacin

Weight accurately 10 mg of indomethacin and was transferd to the 100 ml volumetric flask. add 10 ml of methanol to dissolve it and the volume was made upto 100 ml with demineralised (DM) water as to obtain a stock solution of 100 µg/ml concentration. A dilution of 20 µg/ml was prepared from this stock solution using DM water, as well as the sample was scanned on a Shimadzu 1700 doubling beam UV/visible spectrophotometer between 200 and 400 nm, using DM water as a blank. Figure 2 displays the UV spectrum for the drug sample, indomethacin.

Infrared study of indomethacin drug sample

Indomethacin was compressed into a pellet along with KBr using Shimadzu hydraulic press. The IR spectrum of drug was recorded in the wave number region of 400-4000 cm-1 on an FTIR spectrophotometer (Shimadzu 8400-S) and presented 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 in concentration 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

Solid dispersion technology using mixed-solvency concept includes use of organic solvent. In this method the solubilizers (carrier) are water-soluble where the drug is insoluble in water. In presence of a large amount of solubilizers in water, the drug gets solubilized. Then, water is removed by suitable evaporation techniques to get solid mass (Solid dispersion).

For preparation of solid dispersion in 1:6 ratio, accurately weighed 2.625 gm niacinamide, 3 gm sodium benzoate & 0.375 gm PEG-6000 (so that total weight of the mixture was 6 gm) were taken in a 100 ml beaker and were mixed properly. Then, minimum possible quantity of hot (70-80 °C) demineralized water sufficient to dissolve the above mixture was added, because lesser the amount of water lesser will be the time required to evaporate it and chemical stability of drug may not be affected adversely (during removal of water).

Dissolution of the solubilising agents was facilitated by agitation of Teflon coated magnetic rice bead on a high-speed magnetic stirrer. After complete dissolution of solubilizers, 1 gm of Indomethacin was dissolved in the above solution and temperature was maintained in the range of 55- 60ºC so as to facilitate the evaporation of water. As evaporation proceeded, speed of rice bead automatically decreased and it stopped stirring when most of the water was evaporated, thus indicating the formation of wet solid dispersion. The wet solid dispersion thus obtained was spread on petri-dish and kept in hot air dry oven maintained at 50+ 2ºC so that remaining moisture could also be evaporated easily and a constant weight with no further weight loss (due to evaporation) could be obtained. After complete drying, solid dispersions were crushed using a glass pestle mortar and passed through sieve # 60 and were finally stored in an air tight glass bottle until use. Table 5 indicating a different composition of solid dispersions.

Characterization of solid dispersion

Any method of measuring powder flow must be practical, useful, reproducible and sensitive, and must yield meaningful results. An appropriate strategy is the use of multiple standardized test methods to characterize the various aspects of powder flow as needed by the pharmaceutical scientist.

Following micrometric properties of the solid dispersions were studied:[21]

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

Dissolution rate studies

The solid dispersion or physical mixture equivalent to 20 mg of Indomethacin were tested in dissolution rate studies using U.S.P. (type II) dissolution test apparatus with paddle rotation at 75 rpm. Dissolution studies were conducted in two media, 900 ml of 0.1 N HCl (pH 1.2) and pH 7.2 phosphate buffer. The temperature was maintained at 37+ 0.5°C. then after 10 ml of the sample was withdrawn & analyzed for drug content spectrophotometrically. Add fresh dissolution media for replace withdrawn sample. Calculate the amount of drug & the results of the dissolution studies are shown from 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).

Avicel PH-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.	Solid dispersion (1:6)	140
2.	Avicel PH-112	55
3.	Magnesium stearate	3
4.	Aerosil	2

Evaluation of prepared tablets

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

RESULT AND DISCUSSION

UV Spectrophotometric analysis

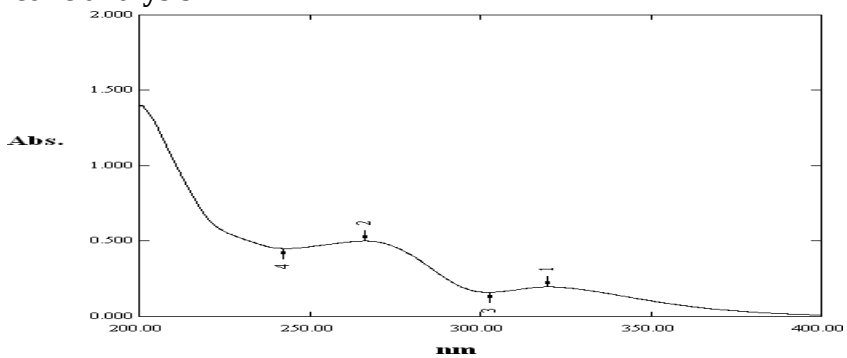
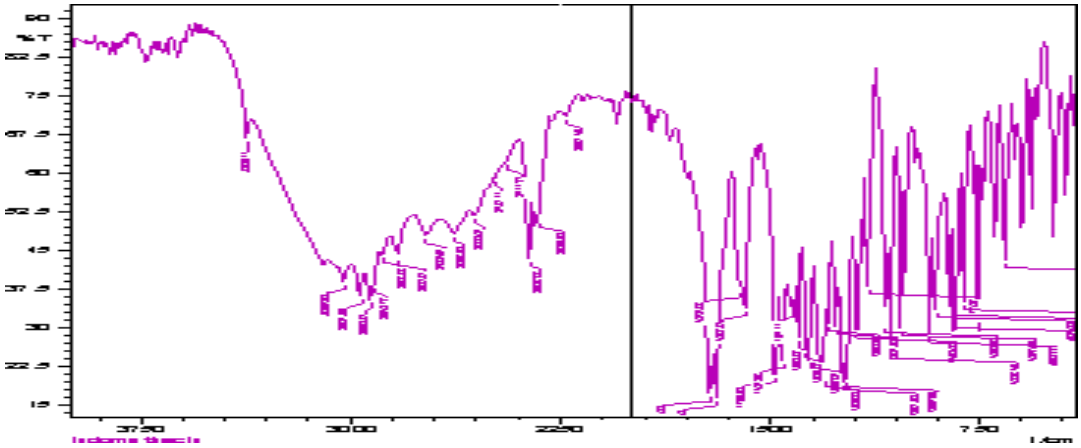


Figure 2: UV spectrum of Indomethacin in DM water

Result: The drug sample exhibited 2 peaks at 265 nm and 320 nm. The peak at 320 nm was selected for analytical purpose.

Infrared study of Indomethacin drug sample



Preparation of calibration curve

Table 3: Absorbance data of calibration curve of Indomethacin

Concentration (µg/ml)	**Absorbance**			
	Set 1	**Set 2**	**Set 3**	**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

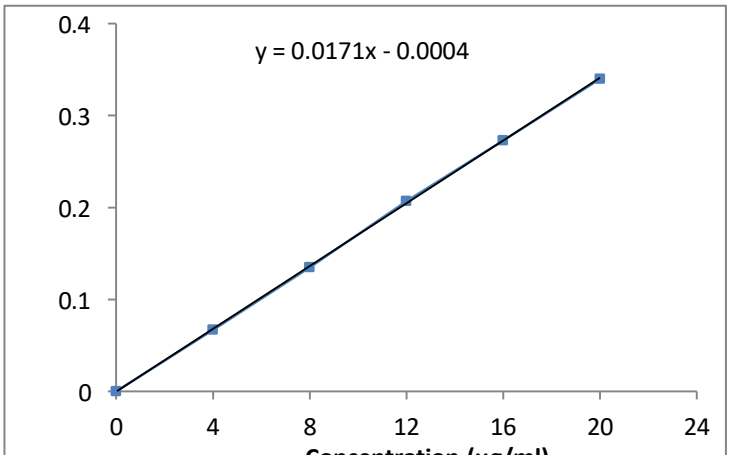


Figure 4: Calibration curve of indomethacin in 0.1 N HCl

Solubility studies in blends containing different solubilizers

Table 4: Solubility of Indomethacin in solutions of individual solubilizer

S. No.	Solubilizer	Average solubility			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

*in solutions containing 40% w/v solubilizer

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	Quantity took (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	Bulk Density (gm/cm^3)	0.534	-
2	Tapped Density (gm/cm^3)	0.656	-
3	Compressibility Index	20.0	Fair
4	Hausner Ratio	1.246	Fair
5	Angle of repose	32º	Good

Result: The values of bulk density and tapped density shows 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 evaluation of Indomethacin tablets

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

Dissolution study of tablets

Table 8: Dissolution of formulated tablets

S.No.	**Time (hr)**	**% Cumulative Drug release**
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

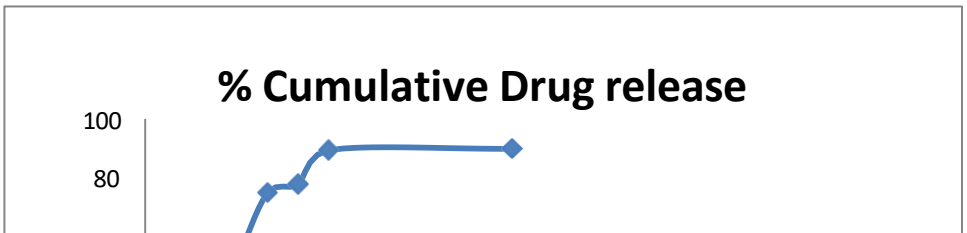


Figure 5: Disoolution of tablet

Stability studies (30 days):

Table 9: Evaluation data of tablets after one month

S.No	**Parameter**	**Results**
1.	General Appearance	Smooth circular disc, elegant.
2.	Weight Variation	pass
3.	Hardness	3.80 ± 0.15
4.	% Friability	0.36 %
5.	Disintegration time	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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