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Formulation and Evaluation of Oral Solid-In-Oil Suspension of Indomethacin

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ABSTRACT

Indomethacin (IND) is a non-steroidal anti-inflammatory drug (NSAID) used to reduce pain and inflammation. It is readily suspended in edible coconut oil in the presence of surfactant. The encapsulated IND in the oil phase of solid-in-oil suspension may reduce the risk of gastric irritation and ulcer associated with conventional oral IND tablets. The present work reports the new solid-in-oil oral suspension formulation of IND and its evaluation parameters. The formulation is investigated for its appearance, organoleptic properties, and content of uniformity, viscosity, drug release, and stability. The developed suspension is compared with the aqueous suspension of IND. The results indicate the suitability of the edible oil for oral delivery of poorly water-soluble drugs in the future.

1. INTRODUCTION:

Indomethacin (IND) is an indole-acetic acid derivative, belongs to the non-steroidal anti-inflammatory drugs (NSAIDs). The IUPAC name of the IND is 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid (Fig.1) [1]. This compound is mostly used as an anti-rheumatic drug and is recommended for the treatment of gout, spondylitis, arthritis, and body pain [2]. It was first discovered in 1963 and at a later stage, the food, and drug administration (FDA) has approved the IND as an analgesic, antipyretic and anti-inflammatory drug [3]. Like other NSAIDs, IND reduces the inflammation caused by prostaglandins [4]. The primary function of the drug is to block the prostaglandin synthesis by inhibiting the synthesis of the enzyme cyclooxygenase (COX), which converts arachidonic acid into prostaglandin [5,6]. Despite high therapeutic efficacy, IND causes various adverse effects including gastrointestinal (GI) irritation, liver complication, ulcer, and renal problems, which leads to the discontinuation of therapy [7-9].

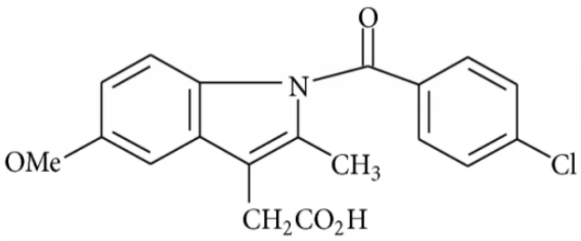

Figure No. 1: Chemical structure of Indomethacin

An oral route is the most convenient method for delivering drugs as it provides easy ingestion, pain avoidance, versatility in manufacturing, and patient compliance. Tablets, capsules, and liquid orals are the most preferred dosage form for the good absorption of the drug in the biological system, fast onset of action, and accuracy in dosing [10]. IND is administered through different routes like oral, topical, rectal, and intravenous. It is practically insoluble in water and poorly soluble in acidic pH and doesn't undergo significant first-pass metabolism [11,12]. IND could be utilized as a classical oral NSAID without any harmful side effects. To achieve this, several oral controlled and sustained-release formulations of IND were already reported with the aim to increase drug retention time in the gastric environment and to release the drug sufficiently during residence time in the intestine [13-15]. The coated tablets of IND were developed using bee glue extract to achieve the controlled release formulation [16, 17]. In another study, IND microspheres were developed

for colon-specific drug delivery systems [18]. However, bitter taste and gastrointestinal adverse effects limit the use of IND [19]. Several attempts have been made in the past few decades to design a novel formulation of IND to minimize the side effect and to get maximum therapeutic efficacy [20,21].

Recently, lipid-based drug delivery systems of poorly water-soluble drugs have gained more attention in comparison with other solid dosage forms. The main objectives are to achieve improved bioavailability, protect the drug from the GI environment and minimize drug-associated adverse reactions [22,23,24]. These lipid-based systems are composed of oils, surfactants, and sometimes co-solvents [25]. Oil solution and suspension, emulsion, and self-emulsifying drug delivery systems are the classical examples of lipid-based formulations [26, 27]. A successful lipid-based formulation requires a suitable lipid vehicle and formulation strategies. Coconut oil is edible oil, mainly used to prepare food. By dispersing IND in coconut oil, it could be possible to mask the bitter taste of the drug and also to improve the retention time in the GI tract without severe adverse effects. However, information is limited about the potential oil-based suspension of IND for oral administration.

In the present study, the new solid-in-oil oral suspension of IND is reported. The drug IND is readily suspended in oil in the presence of surfactant. The oil suspension is characterized and evaluated for its suitability. The results indicate the potential of edible coconut oil for oral delivery of IND and may be useful for other hydrophobic drugs.

2. MATERIALS AND METHODS

2.1. Materials

IND and coconut oil were purchased from Sigma Aldrich, India. Gum tragacanth, Lecithin soya, and sodium carboxymethyl cellulose (CMC) were purchased from HiMedia Laboratories, Mumbai, India. Saccharin was procured from Prism Sales Raipur, India. All other materials used were of analytical grade.

2.2. Preparation of solid-in-oil suspension

The solid-in-oil suspension of IND was prepared as per the reported method with slight modification [28]. The sodium carboxymethyl cellulose was added to preheated oil phase at 60 ºC and stirred at 150 rpm for 25 min and allowed to cool at 45 ºC. Afterward, soy lecithin

was added and get dispersed at a stirring rate of 200 rpm for 15 min. Drug (IND) was triturated along with gum tragacanth and added to the oily vehicle at 30 ºC using a homogenizer for 120 min keeping constant temperature using an ice bath. Saccharin was added and the prepared S/O suspension was allowed to cool at 25 ºC and kept in an air-tight container for further use.

2.3. Evaluation of solid-in-oil suspension

2.3.1. Organoleptic properties

The physical characteristics of the prepared suspension were determined by physical observation. The smell, color, and appearance were examined and recorded [29].

2.3.2. Determination of pH

The pH was determined by using a digital pH meter standardized by testing pH 4 and pH 7 buffers before use. The suspension was placed in a 250 ml beaker and the electrode has emerged directly into the suspension. The pH of formulations was measured from the display of the pH meter. The readings were taken in triplicate and the average value was determined [30].

2.3.4. Sedimentation volume

About 50 ml of suspension is transferred to a 50 ml measuring cylinder and capped with a plug and shaken vigorously for 1 min. The sedimentation volume was measured using the following equation. Where V_1 is the equilibrium volume of the suspension and V_0 is the total volume of suspension before sedimentation [31].

$$\mathbf{F} = \frac{\mathbf{V_1}}{\mathbf{V_2}}$$

2.3.5. Determination of viscosity

The viscosity determination of prepared suspension was carried out using a Brookfield viscometer at room temperature. The method was performed triplicate and average results are presented in centipoise [32].

2.3.6. Redispersibility

The 50 ml of oil suspension was kept in a sample tube and stoppered with a rubber cap. Then the tube was inverted and completely flipped completely until the solution becomes an even suspension. The sedimentation was observed at the bottom of the tube. The minimum number of shears require to redisperse a sedimented suspension is an indicator of redispersibility (N) [33].

2.3.7 Freeze/thaw cycle

To check the effect of temperature the oil suspension formulation was stored at 2 ºC and 40 ºC (hot air oven) for 24 hours. The physical and microscopic changes of suspension were investigated under different temperature conditions [34].

2.3.8. In vitro drug release study

In-vitro release profiles of IND from solid-in oil suspensions were determined by using a beaker method as reported earlier with slight modification [35, 36. 37]. For dissolution, media simulated gastric fluid (HCL, pH 1.2) and intestinal fluid (PBS, pH 6.8) were used. The drug release study was carried out at 37 ± 0.5 ºC, with gentle stirring at 100 rpm. About 10 ml of oil suspension was placed separately in cellophane membrane and placed in two beakers containing dissolution media. An aliquot (3 ml) was withdrawn at every 30 min for 2 h from gastric fluid and 3 h from PBS 6.8 and an equal volume of fresh medium was added to maintain a constant volume of dissolution medium. The absorbance was measured at 270 nm using UV-spectrophotometer. The amount of drug release was calculated from the standard graph.

2.3.9 Stability study

The stability of prepared solid-in-oil suspension of IND was investigated under different stress conditions. The 20 ml sample was placed in small vials and kept in different storage conditions. The studies were carried out for long term storage condition (25˚C ± 2˚C / 60% RH ± 5% for 12 months) and accelerated storage condition (40˚C ± 2˚C / 75% RH ± 5% for 6 months). The suspensions were evaluated in regular intervals and were characterized [38].

3. RESULTS AND DISCUSSION

3.1. Formulation of solid-in-oil suspension

The solid-in-oil suspension of IND was prepared using edible coconut oil. The CMC was used to disperse the drug in coconut oil and gum tragacanth was used to enhance the viscosity of the suspension. Total five formulations of IND (F1, F2, F3, F4, and F5) were prepared by changing the quantity of lecithin and CMC salt (Table1). The optimum stirring speed and ratios were used to develop the formulations. The prepared suspension was used for further studies.

Table No. 1: Formulations IND solid-in-oil suspension

Materials	F1	F2	F3	F4	F5
Coconut oil (ml)	50	50	50	50	50
Indomethacin (mg)	200	200	200	200	200
Lecithin soya (ml)	0.5	1.0	1.5	2.0	0.5
Gum tragacanth (g)	1.0	1.0	1.0	1.0	1.0
CMC salt (g)	0.2	0.4	0.6	1.0	0.8
Saccharin (mg)	30	30	30	30	30
Flavor (g)	0.2	0.2	0.2	0.2	0.2

3.2. Appearance

The formulations prepared were creamy in color with caramel aromas. The physical appearance of oil suspension is given in figure 2.

Figure No. 2: Physical appearance of IND solid-in-oil suspension

3.3. Determination of pH

The pH of the oil suspension was recorded using a digital pH meter. The pH of all suspensions was ranged from 7.01 to 7.31.

3.4. Sedimentation volume

The sedimentation volumes of all the formulations (F1 to F5) were found to be 98.6%, 97.8%, 96.3%, 97.1%, and 97.3% respectively at the end of 24 hours. Examining the suspension after one week, formation of clumpy mass was found in F1, while F2 resulted in clumpy mass after one month. In formulation F3 to F5, sedimentation volume was gradually decreasing from 96.3% to 55.7%, 97.1% to 83.4% and 97.3% to 81.7% respectively. The formulations F4 and F5 revealed good flow from the container. Formulation F4 was found to be stable at the end of 3rd month (Table 2).

Table No. 2: Sedimentation volume of oil suspensions at different time intervals

Formulation	Sedimentation volume (%)				
	24 hours	1st week	1st month	2nd month	3rd month
F1	98.6	CM	CM	CM	CM
F2	97.8	86.4%	CM	CM	CM
F3	96.3	74.7	60.2	58.6	55.7
F4	97.1	91.6	85.1	84.1	83.4
F5	97.3	88.3	85.4	82.8	81.7

Note: CM- Formation of clumpy mass

3.5. Determination of viscosity

The viscosity plays an important role in the stability of a suspension and also influences the flow property of the liquid systems. The viscosity of all the formulations was evaluated by Brookfield viscometer at 25 ºC temperature. The viscosity of formulations is shown in Table 3. The viscosity of all formulations was found to be decreased with an increase in rpm indicated shear thinning nature of the suspension.

Table No. 3: Viscosity of oil suspension of IND at different time intervals

Formulation	Viscosity in cps				
	24 hours	1st week	1st month	2nd month	3rd month
F1	36.6	CM	CM	CM	CM
F2	40.8	41.2	CM	CM	CM
F3	45.8	39.1	29.7	24.5	20.4
F4	47.1	38.4	22.5	17.9	10.5
F5	53.4	36.7	25.8	15.3	10.4

Note: CM- Formation of clumpy mass

3.6. Redispersibility

Ease of redispersibility is an indicator of revolutions require to redisperse a sedimented suspension. The prepared formulations are easily get dispersed by 2 to 3 revolutions which were qualified.

3.7. Freeze/thaw cycle

The prepared formulations were kept at low temperature (2 ºC) and high temperature (40 ºC) to investigate the effect of temperature on suspension. The results were found to be stable and no phase separation and changes in viscosity were observed.

3.8. In-vitro drug release

The preliminary requirement of solid-in-oil suspension is to be able to retain IND in the oil phase after exposure to the gastric environments. The *in vitro* IND release profile from the oil suspension in acidic pH is shown in figure 3. The results showed that the drug release was very less after 2 h study for all the formulations. The IND release was from all the formulations (F1, F2, F3, F4, and F5) was about 5% at the end of 2 hours. This result suggests the entrapment of the drug inside the oil and may reduce GI injuries caused by IND. However, the water solubility of IND in the acidic environment is limited. On the other side, almost complete release of IND from the oil suspension was observed in PBS 6.8 medium (Fig.4). In PBS medium all the formulations released almost 80% drug except formulation F4. About 72% drug was released from F4 after 3 h study. This may be due to the presence of a higher amount of lecithin and CMC in the formulation. However, the formulation F4

was considered a good formulation due to its delayed released property of the IND and selected for further study.

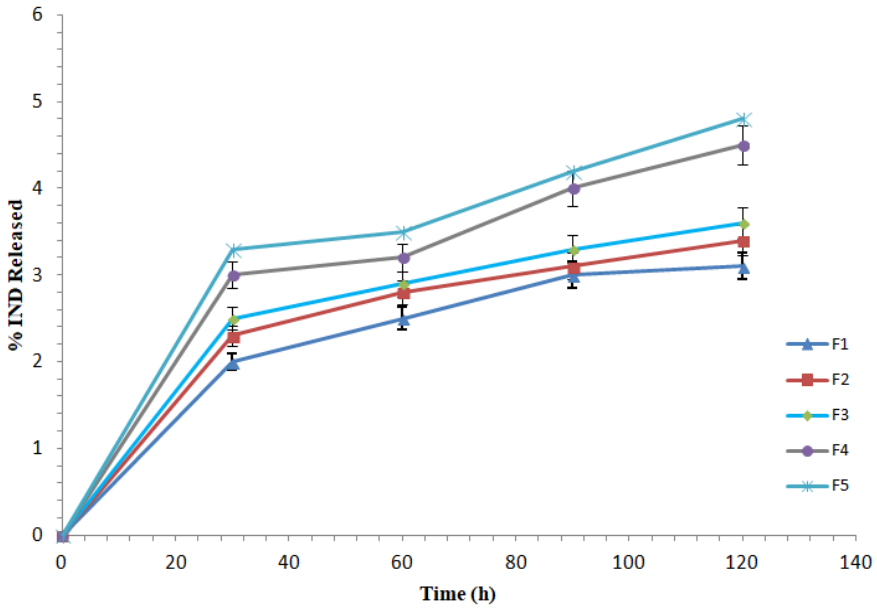

Figure No. 3: *In-vitro* release profile of IND from various oil suspensions in pH 1.2

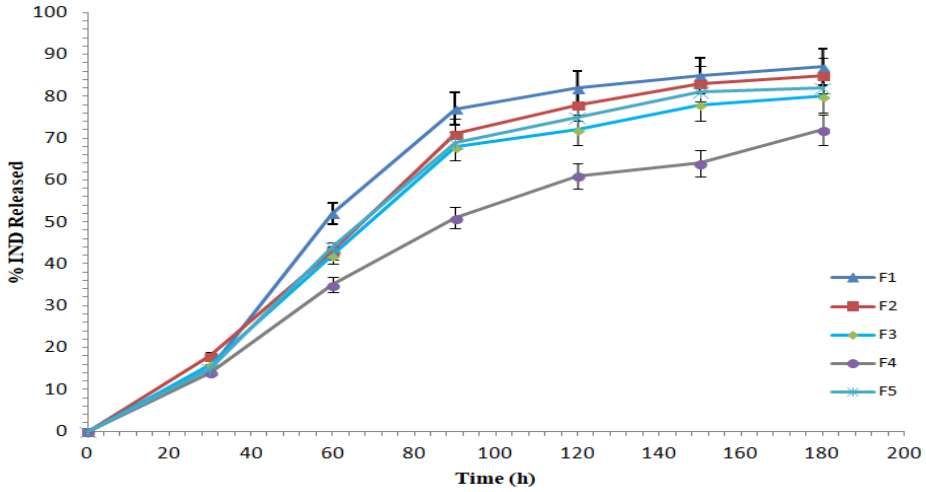

Figure No. 4: *In-vitro* release profile of IND from various oil suspensions in pH 6.8

3.9. Stability studies

The stability, particularly rancidity is a major issue for any oily formulation. To study the effect of temperature and moisture the formulation F4 was placed under different stress conditions (25˚C ± 2˚C / 60% RH ± 5% and 40˚C ± 2˚C / 75% RH ± 5%). After six months

of study, the pH of the formulation F4 become acidic at high temperatures and high humidity. This may be due to the leaching of drugs from oily vehicles. There were no noticeable differences observed in viscosity and dispersibility when stored at both temperature and humidity conditions. There was a slight decrease in drug concentration at high temperature after 3 months, which might have been caused by the degradation of oil at high temperature. Apart from this, no significant change in drug concentration was observed during the study. The results of the stability test indicated that the solid-in-oil suspension exhibited good physiochemical stability when stored at 25˚C ± 2˚C / 60% RH ± 5% condition.

4. CONCLUSION

The developed solid-in-oil suspension of Indomethacin will be a good alternative to the existing tablet or capsule for oral administration of the drug, which may reduce GI injuries. This delivery system may be applicable for both poorly soluble and aqueous soluble drugs. From the present study, it can be assured for the suitable design and development of oil-based suspension. It will also be useful for the drugs like antibiotics and other lifesaving drugs which are not stable in aqueous suspension. The study further suggests the development of the new delivery system of other NSAIDs that are reported either severe gastric irritation or instability in an acidic environment.

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