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Investigations on a Novel Method for the Formulation of Solid Dispersions Part II – Aqueous System, Characterization and *In-Vivo* Studies

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ABSTRACT

Solid dispersions method for the improvement of solubility of lipophilic drugs has wide acceptance. Indomethacin (IMC) formulations F2 and F5 were selected to be reformulated in an aqueous system. The aqueous stability of both the formulations was determined in Phosphate buffer pH 5.0 to 8.0. The aqueous dispersions of both the formulations were formulated in pH 7.0 and freeze dried and coded as F2B and F5B. The freeze dried solid dispersions were evaluated for percent recovery, drug content determinations, and dissolution studies. The formulation F5B showed marked enhancement of dissolution in USP-NF dissolution media. The thermal analysis was done using modulated DSC and the molecular interactions were established using FTIR spectroscopy. The formulations were evaluated for *in-vivo* anti-inflammatory activity by measuring decrease in edema using Rat Paw method. The DSC results indicated the uniform distribution of IMC amorphously in the carrier. No physicochemical interactions were found between drug and excipients on FT-IR spectroscopic studies. A rise in anti-inflammatory activity was found with freeze dried formulations in comparison to reference IMC.

INTRODUCTION

The commencement of drug action depends on the dissolution and subsequent absorption of drug into the blood [1]. Since the dissolution is the rate limiting step in the intestinal absorption of lipophilic drugs, most of the drugs; almost 40 % available in the market are lipophilic, practically insoluble in water, have shown to take long time for the start of onset of action[2,3]. As per biopharmaceutical classification system, drug is considered insoluble if the highest unit dose remained non-soluble in 250ml of aqueous media pH 1 and 8[4]. Several techniques like particle size reduction, hydro- trophy, complexation, solubilization(surfactants) and solid dispersions are widely used to increase the dissolution rate of these drugs [2, 3].

In the recent years, the solid dispersion technique has proved to be very successful in achieving the goal of dissolution enhancement of many lipophilic drugs. Several formulations based on solid dispersions have been approved by USFDA [5]. Solid dispersions technique is based on the principle of dispersing lipophilic drug at the molecular level into the hydrophilic polymer(s); thereby enhancement of dissolution has been achieved by increasing the hydrophilicity of the drug without altering the structure of it [6]. Solid dispersions are prepared by hot melt method in which the drug and polymer(s) are melted, mixed together and cooled [7]. The second solvent evaporation method in which both drug and polymer are dispersed and the solvent is removed by various evaporation techniques [8]. Both of these methods have major drawbacks like chances of drug decomposition at high temperature, non-uniform mixing in hot melt method and the necessity of using low boiling point organic solvents like alcohol, acetone, methylene chloride, ethyl acetate and mixture of these, in solvent evaporation method, which are costly, hazardous to environment and to the preparation as traces of these will remain in the formulation [9]. Further processes with organic solvents require explosion proof processing equipments as well as recovery rooms [10].

Lyophilization method of solvent removal is a promising method employed in the preparation of several solid dispersion systems by solvent evaporation method because the preparation is subjected to minimum thermal stress[10].The method involved freezing of drug polymer solution and subsequent drying at low temperature from frozen state. The major problems associated in the applications of this method with organic solvents are; the inability to freeze

organic solvents during sublimation and time consumption as the process takes 48h-72h [11, 12].

Indomethacin a non-steroidal anti-inflammatory drug used in the treatment of inflammation and arthritis; has been selected as model drug in the present investigation because it is highly lipophilic (log P value 4.27) and practically insoluble in water (0.937mg/l); belongs to BCS class II drug. (http://www.drugbank.ca/drugs/DB00328).

Several research attempts have been made to boost the solubility and dissolution of indomethacin by solid dispersion technique using hot melt method. Hydroxypropylmethyl cellulose 4000cps (HPMC), Polyvinylpyrrolidone K30(PVP) are the two carrier polymers; used in the present study are frequently used in the formulation of solid dispersions (part –I).

The present research exploration is an effort to design and confirm a suitable aqueous non-alcoholic system based on purified water that can be used in the preparation of solid dispersions by freeze drying method. Formulations F2 and F5 selected from our previous study(part-I) was used in the present investigation for reformulation.

MATERIALS AND METHODS

Indomethacin (IMC), Polyvinylpyrrolidone K 30(PVP K 30) and hydroxypropylmethylcellulose (HPMC) were purchased from UFC Biotechnology, Amherst, USA. Phosphate monobasic, sodium hydroxide pellets and ethanol (99.9% HPLC grade) were purchased from Sigma-Aldrich USA. All the chemicals used in the experimental study were of analytical grade and utilized as received.

1. Stability of Indomethacin formulation in aqueous system

0.5g equivalent of IMC in formulation F2 (IMC: HPMC; 1:1.5) and F5 (IMC: PVPK30; 1:1.5) was accurately weighed in phosphate buffer 7.0 with stirring at 200rpm for 2 h on magnetic stirrer. The solution was transferred in to screw capped clear glass bottle and equilibrated for 48h on oscillating shaker maintained at 150 rpm. After 48 h the solution was placed under laboratory conditions. Saturated solution of IMC 0.5%w/v in phosphate buffer pH 7.0 was prepared in the same manner; was used as reference standard [13]. At the interval of 7 days, 1 ml of 0.05% w/v of respective IMC solution was withdrawn and diluted to 250ml with phosphate buffer pH 7.0 in a volumetric flask. The absorbance of the solution was

measured as a function of time, spectrophotometrically at 320 nm. The test was carried in duplicate and average value of the two was recorded. The procedure was repeated using phosphate buffer pH 5.0, 5.4, 6.0 and 8.0.

2. Preparation of drug-polymer solution

F2 (IMC: HPMC; 1:1.5) and F5 (IMC: PVPK30; 1:1.5) containing equivalent of 0.5g of IMC was added into the solution of Phosphate buffer pH 7 slowly with continues stirring for 2 hr. The solution was transferred into 100ml clear glass screw capped bottle. The solution was equilibrated on oscillating shaker, speed 150 rpm for 48h. The procedure was repeated with pure IMC in phosphate buffer pH 7 used as reference control. The formulations were coded as F2B, F5B and RC respectively.

3. Lyophilization

The prepared solutions were, frozen at -30^{o}C for 24h, dried by two stage lyophilization (Freeze drier Christ Beta 2-8 LD Plus, Martin Christ Germany). First stage, the main drying was done at condenser temperature -20^{o}C, vacuum 1 mbar for 12 hr. At second stage which followed first stage automatically, the final drying was done at condenser temperature -31^{o}C, vacuum 0.34 mbar for 12hr. The lyophilized solid dispersions (LSDs) were stored in screw capped clear glass bottles sealed with paraffin film.

4. Percent Recovery

The percentage yield of prepared formulation F2 and F5 was determined using following equation[14-16]

$$PR = \frac{W1}{W2} X100$$

Where: W1 is the weight of solid Dispersion formulation

W2 is the weight of solid dispersion formulation+ Phosphate buffer

5. Drug Content determination

Accurately weighed LSDs equivalent to 50mg of IMC was dispersed in 10ml of purified water and it is gently shaken for 15 minutes. 50 ml methyl alcohol was added and the solution

was shaken well. Sufficient methanol was added to produce 100ml. filter the solution, to the 5ml of filtrate, a mixture of equal volume of methanol and phosphate buffer pH 7.2 was added to produce 100ml (0.025mg/ml). The optical density (A_T) of the solution was determined at 320nm by using Evolution 60S UV-visible spectrophotometer[17].The absorbance (A_s) of indomethacin RS standard solution (0.025mg/ml) prepared with same procedure as described was measured. The content of IMC in LSDs was calculated with following equation.

$$Content_{LSD} = \frac{A_T}{A_S} X\ C_{std}$$

$C_{std} = Standard\ content\ of\ IMC\ in\ mg(50mg)$

6. *In-vitro* release studies

Dissolution investigations were performed on filled capsules containing the LSDs equivalent to 0.5g of IMC. The testing was done with USP basket apparatus Type I; Erweka Germany. The dissolution media used was 750ml ofUSP-NF media pH7.2, paddle rotation speed 50rpm; maintained at 37^{o}C±0.5 [17]. The test was performed for 1 h; 10ml sample was withdrawn, substituted with pre warmed media, at 30minutes time interval, filtered, diluted to 50 ml with the dissolution media and the absorbance of the solution was measured at 320nm. The percentage drug dissolved was calculated from Specific absorbance $\left(A_{1cm}^{1\%}\right)$ of indomethacin RS [17]. The dissolution testing was also done in purified water as dissolution media. The test was done in duplicate and average value of the two was recorded.

7. Differential Scanning Calorimetry (DSC): Thermal behavior of IMC, LSDs were recorded by differential scanning calorimeter, Modulated DSC VI.1A was used with an argon purge at 45cc/min in order to determine the melting endotherm on set temperature. Samples were heated at 10^{o}C/min under argon atmosphere in the 30-350^{o}C. The instrument was calibrated for temperature and enthalpy with indium [18, 19].

8. Fourier Transform Infrared Spectroscopic studies (FTIR)

Spectrum of IMC and LSDs was recorded on Cary 630 FTIR spectrophotometer, Agilent technology. The IR determinations were carried out in the scanning range of 4000-500cm^{-1}[19-21]

9. *In-vivo* Anti-inflammatory Activity

The experimental *in-vivo* study was performed in the pharmacology lab of our institute under the supervision of institutional ethical committee for the safe use of animals established under CPCSEA (committee for the purpose of control and supervision of experiments on animals) guidelines, Lic no: 1606/PO/a/12/CPCSEA.

The *in-vivo* experimental anti-inflammatory activity of the prepared IMC formulations F2B and F5B was evaluated by Inflammation Induced Rat Paw method[22-24]. The study was conducted on male wister rats weight 100g to 200g. The rats were shifted into cages acclimatized for 7 days under controlled temperature and humidity in the experimental laboratory. The rats were kept on restricted diet of animal feed and tap water.

The animals were divided into three investigational groups and coded as F2B, F5B and RC. Each group consists of five rats. The rats were kept on free access to diet and water before and throughout the study period so as to minimize the gastrointestinal effects of the formulations administered.IMC formulations F2B and F5B equivalent to the dose of 1mg/kg body weight was administered orally to each rat in respective groups F2Band F5B. The reference group 'RC' was administered orally pure IMC LSD formulation at the dose of 1mg/kg.

The edema was produced by injection of 0.2 ml undiluted albumin in the left hand paw of each rat. The respective formulation was administered 30 minutes of the injection. Before and after the treatment at the interval of 30 minutes for 6 hours; the volume of displaced distilled water by inflamed paw was measured by digital plethysmometer model PLM 02Plus with accuracy ±0.005ml and resolution 0.001ml. The percentage decrease in edema following administration of respective formulation was determined using following equation.

$$DE = 1 - \left\lfloor \frac{T - X}{R - Y} \right\rfloor x100$$

Where "DE"- % Decrease in edema

"T" – Mean paw volume of treated rats; X- Mean paw volume of untreated rats before albumin injection

"R"- Mean paw volume of treated rats in reference group; Y- Mean paw volume of untreated rats before albumin injection.

RESULTS AND DISCUSSION

Stability of IMC formulations in Aqueous Media

The figure 1A and 1B depicts the effect of pH on the aqueous stability of IMC formulations F2 and F5. At day 1 the 57% of IMC dissolved at pH 5, 64 % at 5.4, and 80% at pH 6 while 100% IMC dissolved in pH 7 and pH 8. At ph 5, 5.4 and 6 the concentration of IMC decreased progressively indicated by the settlement of precipitation of IMC in the aqueous solution at the bottom of solution after 28 days. The % concentration of more than 95% was found for Both F2 and F5 formulations at pH 7 after 28 days. The highest IMC decomposition was found at pH 8 which was indicated by less than 5% concentration of IMC after 28 days. The logK (day^{-1}) values for RS F2 and F5 were plotted against pH of aqueous solution figure 1C.The log K value for F2 was found lowest at 0.00079 at pH7 followed by RC at 0.0019 and F5 at 0.016 indicated highest stability of formulation F2 at pH7.The highest value of log K (day^{-1}) 0.139, 0.106 and 0.114 for RS, F2 and F5 was found at pH 8 indicated fastest rate of decomposition. The polymers HPMC and PVPK30 significantly decrease the rate of decomposition of IMC improve the stability pH 8 in comparison to RC as indicated by K values. IMC showed the fastest rate of decomposition at pH 8 from pH range 5 to 8. The polymers played an important position in preserving the entrapped drug molecules within the amorphous state regardless of the reality that the exact mechanisms of stabilization in strong molecular dispersions are nonetheless no longer absolutely understood. Formulation F2 and F5 in Phosphate buffer pH7 was selected for further experimental investigations.

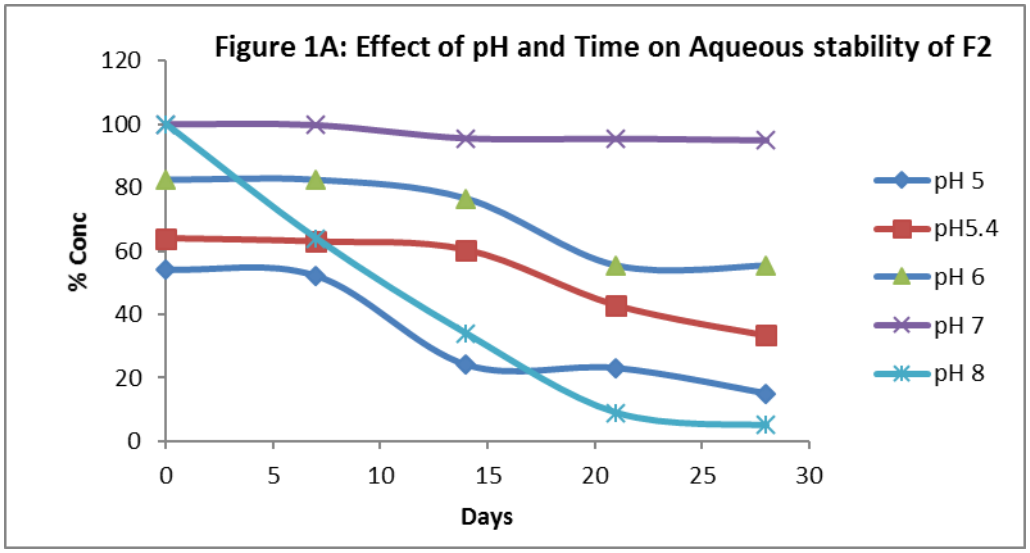


Figure 1A: Effect of pH and Time on Aqueous stability of F2
120
100
80
60
40
20
0
% Conc
0
5
10
15
20
25
30
Days
pH 5
pH5.4
pH 6
pH 7
pH 8

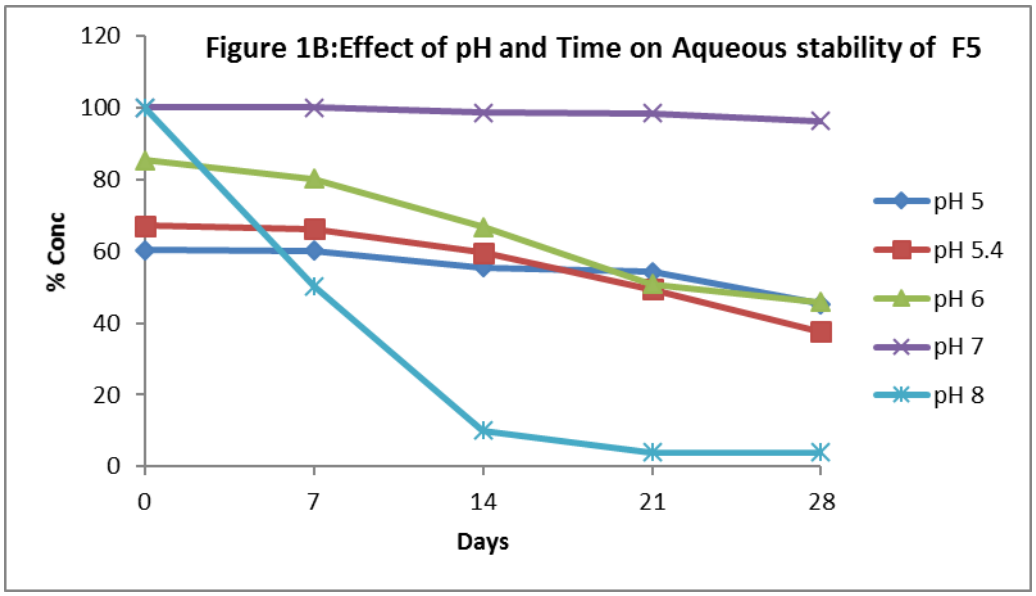


Figure 1B:Effect of pH and Time on Aqueous stability of F5
120
100
80
60
40
20
0
% Conc
0
7
14
21
28
Days
pH 5
pH 5.4
pH 6
pH 7
pH 8

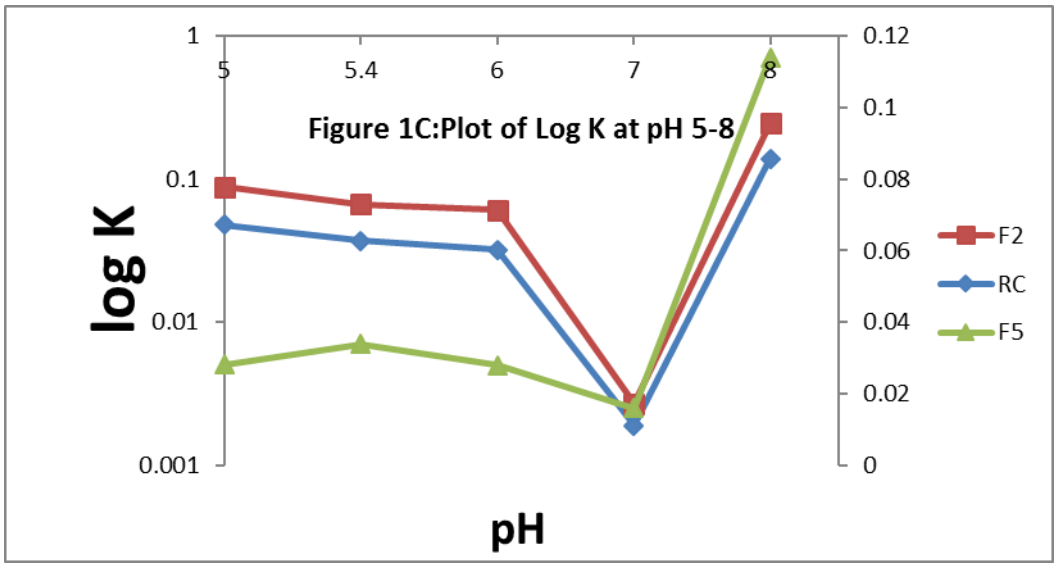


Figure 1C:Plot of Log K at pH 5-8
1
0.1
0.01
0.001
log K
5
5.4
6
7
8
pH
0.12
0.1
0.08
0.06
0.04
0.02
0
F2
RC
F5

Percent recovery

The solid dispersions formulations were removed from the freeze drier and kept at laboratory conditions for 24 hrs. The contents were removed from the bottles and weighed. The amount of formulation F2B and F5B was 99.78% and 98.32% respectively.

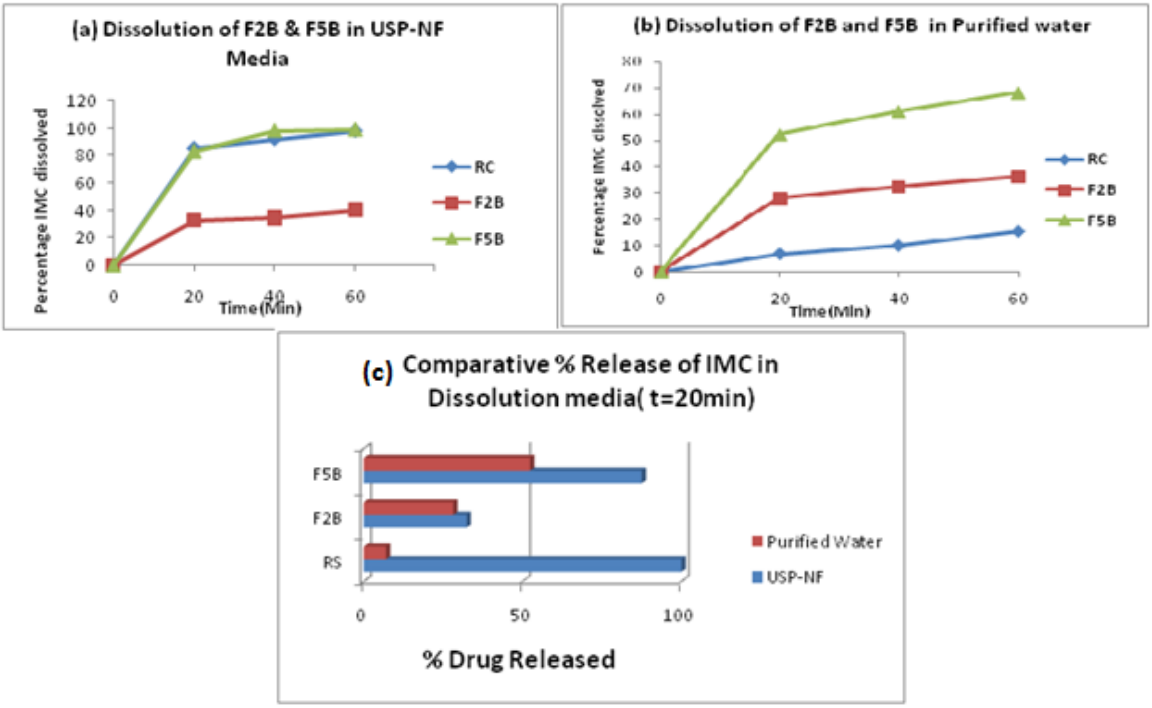
Drug Content Uniformity

The IMC content in solid dispersion formulations F2B and F5B were found 98.76% and 99.24% (n=3) respectively.

***In-vitro* Dissolution Studies**

Figure 2a represented the dissolution profile of LSDs in USP- NF media. In USP-NF media; more than 80% of IMC was released for formulation RC and F5B after 20 minutes, hence complied the USP-NF dissolution test for IMC capsules. There was only 32.42 % of IMC released form formulation F2B. At 60mins, maximum 39.84 % of IMC was released from F2B. The dissolution profile of IMC formulations F2B and F5B in purified water was represented in figure 2b. At 20 mins, the percentage IMC dissolved for RC, F2B and F5B was 7.0, 28.23 and 53.35% respectively. At 60 mins the percentage drug dissolved was 10.15, 36.35 and 68.26% respectively for RC, F2B and F5B. It was found that more than 50% of the drug was released from formulation F5B at 20 mins which was 7 times higher in comparison to RC (figure 2c). The dissolution of IMC in purified water was nonlinear with time as only 18% of drug was released in 40 mins from 20 to 60 mins for formulation F5B, followed by 8% for F2B and RC. The slow release of IMC from F2B was due to the formulation of matrix gel; a property of HPMC in which the IMC molecules interpenetrated failed to get released into the dissolution media. This pattern of dissolution behavior for HPMC based formulations in USP-NF dissolution media indicated that the dissolution of IMC from HPMC hydrogels is regulated through a selection-managed mechanism wherein the hydrogel matrix is insoluble and the dissolved amorphous drug (changing into relatively supersaturated drug solution) slowly diffuses out of the hydrogel network [25,26]. Both the formulations failed to release more than 80% of IMC in purified water, required by USP-NF limit of dissolution test for IMC capsules.

Figure 2 : Dissolution profile of LSDs



Differential Scanning Calorimetry (DSC):

The DSC thermograms of IMC formulations RC, F2B and F5B were represented in figure 3. A strong endothermic peak for IMC was observed at 159.3ºC in formulation RC. A less intense broad peak for IMC was observed in formulation F2B. There was complete absence of endothermic peak at 159.3ºC was found in F5B, indicated that the drug is amorphously distributed in the carrier. The exothermic peak at100ºC was found in all the formulations pertain to the dehydration of water molecule in the monobasic potassium phosphate buffer system. The strong endothermic peak at 253.5ºC was found in all the formulations indicated the melting of monobasic potassium phosphate. At temperature higher than 325ºC, there was decomposition of IMC observed in formulation RC. The IMC was found to remain stable at temperature higher than 325ºC in F2B and F5B indicated the improved thermal stability of IMC by HPMC and PVP respectively.

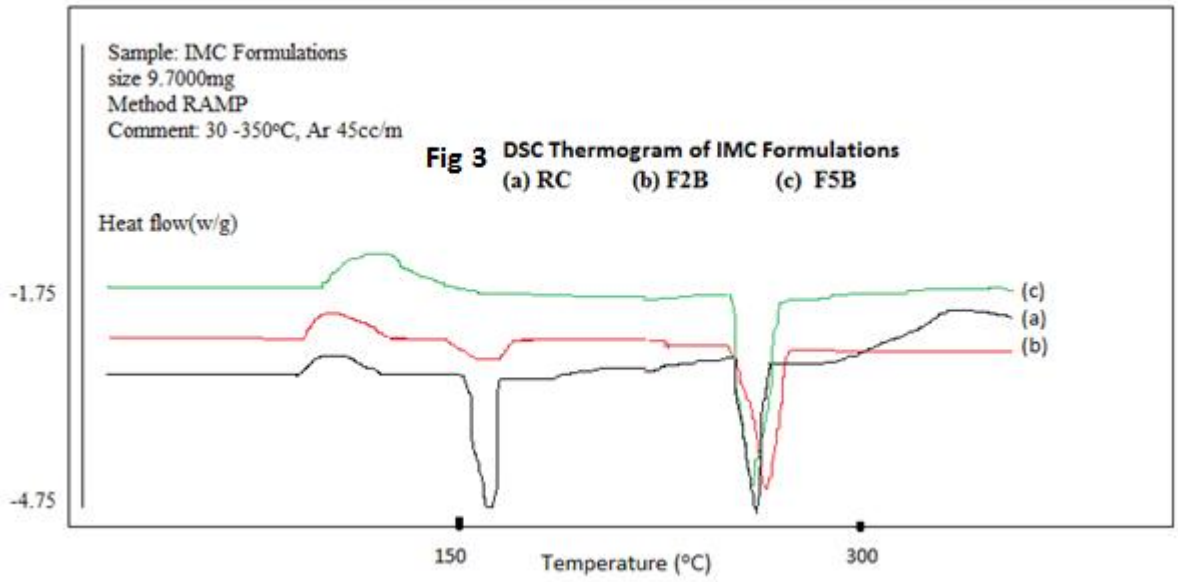


Fig 3 DSC Thermogram of IMC Formulations
(a) RC (b) F2B (c) F5B

Fourier Transform Infrared Spectroscopic studies (FTIR)

Figure 4 represented the FT-IR spectrum of RC, F2B and F5B. Characteristic absorption peaks were appeared at frequencies 2967cm^{-1}, 2928cm^{-}1, 1713cm^{-1}, 1689cm^{-1}, 1590cm^{-1}, 1480 cm^{-1} and 1307cm^{-1} in the spectra of RC. Absorption peaks at 2967 cm^{-1} and 2928 cm^{-1} were due to C-H stretching of methyl groups and aromatic rings. Peaks at 1713cm^{-1} and 1689cm^{-1} were due to the C=O stretching of two carbonyl groups pertaining to benzoyl and acidic group. Peaks due to C=C stretching of aromatic rings were found at 1590cm^{-1} and 1480cm^{-1}. Strong absorption peak at 1307cm^{-1}was observed due C-N stretching. No extra peaks were appeared in the spectra of prepared F2B and F5B indicated that chemical interactions between the drug and the excipients.

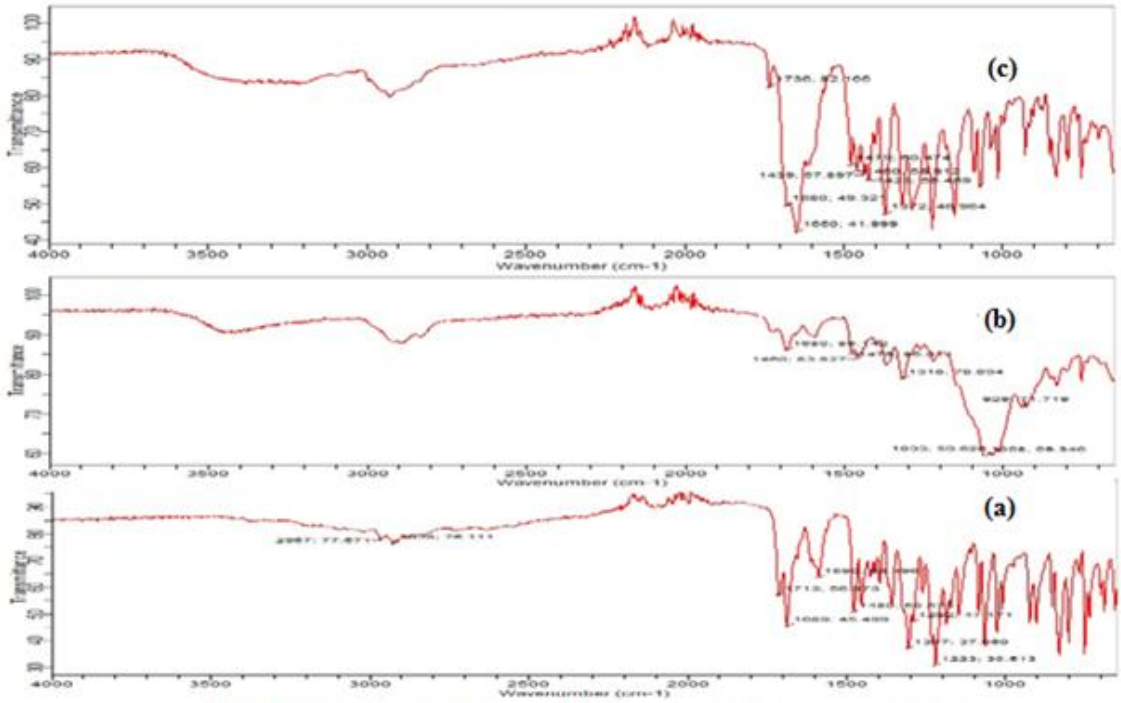


Figure 4 : FT-IR Spectrum of (a) RC (b) F2B (c) F5B

***In-vivo* Evaluation**

Data pertained to the anti-inflammatory activity of LSDs was presented in Table 1 for RC, F2B and F5B. The IMC formulations F2B and F5B showed a significant increase in anti-inflammatory effect, in the egg albumin activated paw edema as in contrast to the pure IMC as reference standard. IMC prevents inflammation by antagonizing the COX enzyme required for prostaglandins synthesis.

The preparations exhibited the maximum edema inhibition ideologically significantly different from the control ($P < 0.05$), demonstrated that the bioavailability of the administered LSDs formulations is greater than the pure drug. At 0.5 hr the formulation F2B and F5B inhibited 32% and 42% edema in comparison to 15% by pure IMC which is RC. For this result, it was found that there was 27% increase in anti-inflammatory activity was observed with formulation F5B while 17% increase with formulation F2B. The formulations F2B and F5B decreased the edema by more than 50% in 1 hr. At 6 hr, both the formulations reduce the edema by more than 80% in contrast to pure IMC which decreased the edema by 68%. This indicated that the rate of dissolution and subsequently absorption of IMC from the formulations F2B and F5B in the rat intestine was quick, greatly enhanced. This led to

decrease in onset time for drug action is influenced by the carrier, surfactant and the phosphate buffer.

The graph %DE Vs Time was depicted; showed that the formulation F5B based on PVP carrier was good in reducing the edema when compared with RC and F2B.

Table 1: %DE (PVE* ±SD) data for IMC Formulations F2B and F5B.

Time	RC	F2B	F5B
	%DE(PVE* ±SD)	%DE(PVE* ±SD)	%DE(PVE* ±SD)
0.5	15(1.23±0.75)	32(0.98±0.19)	42 (0.92±0.44)
1	37(0.98±0.36)	52(0.88±0.43)	59 (0.72±0.21)
2	46(0.97±0.47)	67(0.79±0.32)	73(0.61±0.34)
3	64(0.83±0.24)	78(0.68±0.17)	83 (0.55±0.25)
4	67(0.85±0.25)	79(0.60±0.24)	87(0.49±0.11)
5	67(0.86±0.49)	82(0.59±0.14)	93(0.48±0.24)
6	68(0.82±0.55)	82(0.58±0.42)	93(0.47±0.23)

*** PVE-Paw Volume Edema; Mean±SD (n=3)**

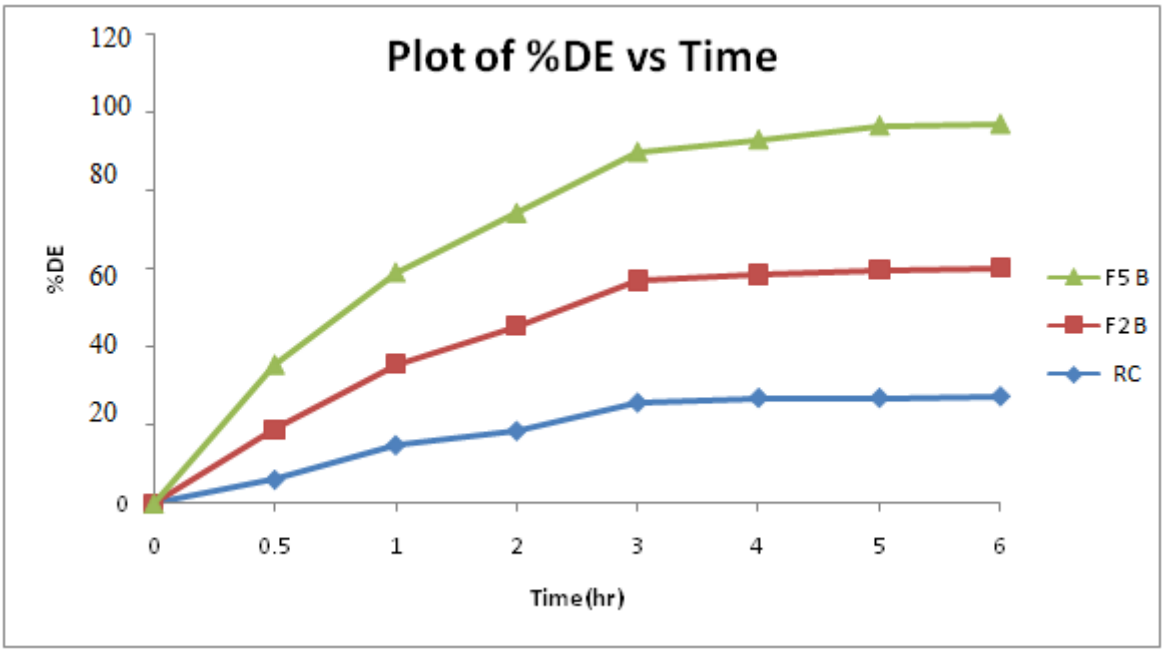


Figure 5: The graph %DE Vs Time was depicted

CONCLUSION:

The aqueous media processed lyophilized IMC formulations of IMC formulations F2B and F5B showed enhanced dissolution in purified water in comparison to reference formulation 'RC' processed under same conditions. A more than 7% dissolution enhancement was found with F5B in purified water. The formulation F2B failed to complied dissolution test limit in USP-NF media for IMC capsules. This enhancement of dissolution is due to the increased hydrophilicity coupled with amorphous distribution of the drug in the hydrophilic carrier as indicated by the DSC. There were no molecular interactions observed between the drug and the carriers. The anti-inflammatory activity of F5B was increased by 27 % in comparison to RC that indicated the better and fast absorption of solid dispersion formulations.

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