ejpmr, 2017,4(10), 410-421

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

EFFECT OF EUDRAGIT® POLYMERS (RS 100 AND RL100) ON THE RELEASE OF DICLOFENAC SODIUM FROM MICROCAPSULES

***Sonika Rani Jangra and D.C. Bhatt**

Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar, India.

***Corresponding Author: Dr. Sonika Rani Jangra**

Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar, India.

Article Received on 20/08/2017 **Article Revised on 10/09/2017** **Article Accepted on 01/10/2017**

ABSTRACT

The controlled release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. The micro-encapsulation is one of the widely accepted technique for the controlled drug delivery. Polymers used as in formulation play a vital role in controlling the drug release from the microcapsules. Diclofenac Sodium, is a widely used nonsteroidal anti-inflammatory drug (NSAID) taken or applied to reduce inflammation or for reducing pain in certain conditions. It is used commonly to treat mild to moderate postoperative or post traumatic pain, when inflammation is present. Diclofenac Sodium is BCS class II drug and it was microcapsulated by the solvent evaporation technique using a nonaqueous solution of polymers Eudragit® RS100 and Eudragit® RL100 to achieve its sustained release from the microcapsules at a slower rate. The effect of two copolymers Eudragit® RS100 and Eudragit® RL100 was investigated using various drug polymer ratio. These microcapsules were free-flowing in nature with smooth surface, spherical shape as examined by scanning electron microscopy. The data obtained from *in vitro* dissolution profiles of drug formulations were compared using different release kinetics models and the regression coefficients were compared.

KEYWORDS: Microencapsulation, Eudragit, Sustained Release, Diclofenac Sodium.

INTRODUCTION

Microencapsulation is a process by which very tiny droplets or particles of liquid or solid material are surrounded or coated with a continuous film of polymeric material to obtain microcapsules.

The first research leading to the development of microencapsulation procedures for pharmaceuticals was published by Bungenburg de jong and Kaas in 1931 (Deasy Patrick B.,2007) which dealt with the preparation of gelatin spheres and the use of a gelatin coacervation process for coating.

Microcapsules have a number of benefits such as converting liquids to solids (of altering colloidal and surface properties), separating reactive compounds, providing environmental protection, improved material handling properties. Microcapsules usually have a particle size range in between 1-2000µm (Benita Simon, 2014).

The uniqueness of microencapsules is the smallness of the particles and their subsequent use and adaptation to a wide variety of dosage forms and product applications. Because of the smallness of the particles, drug moieties can be widely distributed throughout the gastrointestinal tract,thus potentially improving drug sorption (Banker GS and Rhodes CT, 2002).The material inside the microcapsule is referred to as the ***core***, internal phase or fill, where as the wall is sometimes called a ***shell***, coating or membrane (Mahmood Ahmad *et al*, 2011) and (Nitika Agnihotri *et al*, 2015).

Eudragit® In the year 1954 first two polymers Eudragit L and Eudragit S for enteric coating were launched. For rapidly disintegrating and sustained release coatings Eudragit based products were added during the 1960s, expanding the potential applications. The aqueous polymer dispersion forms of Eudragit were introduced in 1972, making the process of coating easier, safer, more versatile and economical. With the development of various grades of Eudragits, it became possible to handle many aspects of formulation development such as film coating, granulation, direct compression, melt extrusion gastrointestinal targeting, enteric coating, pulsed release and transdermal formulations.

Eudragit® polymers can be used individually as well as in combination in one coat or by layering several film. They offers high degree of formulation versatility, therefore they can be combined with a wide variety of other excipients'. The ability to combine Eudragit® polymers also gives possibilities for ensuring, that the drug ultimately unfolds its full potential in the right

location at the right time for maximum therapeutic effect.(5)

Eudragit® polymers are available in various forms (Table 1) to facilitate handling and processing as well as maximize application-specific benefits

- Aqueous dispersions.
- Organic solutions.
- Granules.
- Powders.

Advantages of Eudragit® polymers

- High pigment binding capacity.
- Reliable functionality at very low coating levels.
- Good compressibility.
- Smooth coating surface.
- High yield.
- High thermal stability.
- Polymer combinations feasible.
- Multiple layer coatings.
- Excellent adhesion.

Benefits of Eudragit® for enteric coatings

- Gastro resistance
- pH-controlled drug release
- Gastrointestinal targeting
- Colon delivery
- Protection of acid-sensitive actives
- Protection of gastric mucosa from aggressive actives
- Increased drug effectiveness
- Excellent storage stability

Table. 1: Eudragit® Polymers and their characteristics.

Product	Availability	Dissolution Property
Eudragit® RL100	Granules	Insoluble High permeability pH-Independent swelling
Eudragit® RL PO	Powder	
Eudragit® RL 30 D	Aqueous dispersion	
Eudragit® RL 12,5	Organic solution	
Eudragit® RS100	Granules	Insoluble Low permeability pH-Independent swelling
Eudragit® RS PO	Powder	
Eudragit®RS 30 D	Aqueous dispersion	
Eudragit® RS12,5	Organic solution	
Eudragit®NE 30D	Aqueous dispersion	Insoluble, low permeability pH-Independent swelling No plasticizer required Highly flexible
Eudragit® NE 40D	Aqueous dispersion	
Eudragit® NM 30D	Aqueous dispersion	

Diclofenac Sodium is a widely used nonsteroidal anti-inflammatory drug (NSAID) taken or applied to reduce inflammation or for reducing pain in certain condition. It belongs to the group of aryl acetic acid derivatives. Diclofenac sodium is used commonly to treat mild to moderate postoperative or post traumatic pain, when inflammation is present. Diclofenac Sodium is a BCS class II drug having a low water solubility which is the limiting step for absorption and bioavailability. Various techniques such as solid dispersion, liquisolid, mixed solvency approach have been reported for enhancement of the solubility.[4,9,11]

Diclofenac Sodium possesses narrow therapeutic index due to its short biological half life (1.15-2hrs) and it gets eliminated from plasma compartments within few hours, so frequent administration is necessary to maintain its therapeutic concentration. Exposure of stomach to high level of Diclofenac Sodium can cause gastrointestinal damage such as ulceration or bleeding, it requires immediate termination of treatment. Therefore, Diclofenac Sodium is a suitable candidate for the formulation of sustained/controlled release microcapsules, resulting in less frequent dosing and less gastrointestinal disturbance.[19]

MATERIALS AND METHODS

Material and methods

Diclofenac Sodium was obtained as a gift sample from Arbro Pharmaceuticals Pvt. Ltd., New Delhi, India. Eudragit® RS100, Eudragit® RL100 and Sodium alginate were procured from Central Drug House Pvt. Ltd., New Delhi. Span 80, Magnesium stearate, Liquid paraffin were obtained from High Purity Laboratory Chemicals Pvt. Ltd., Mumbai . Acetone, Hydrochloric acid were obtained from S.D. Fine-Chem Limited, Mumbai.

Preparation of Microcapsules

Microcapsules of Diclofenac Sodium were prepared by solvent evaporation technique by using Eudragit® RS-100 and Eudragit® RL 100 as coating materials.(15-18).

Solution ‘A’ - Eudragit® RS-100 and Eudragit® RL 100 were dissolved in different ratios in 20 ml acetone to form a homogenous polymer solution. Diclofenac sodium (100mg) was dispersed in it and mixed thoroughly. Solution ‘B’- Liquid paraffin (100ml) containing 1%(w/w) span 80, magnesium stearate (80mg) and (0.005-0.6g) sodium alginate. This Solution‘A’ was slowly poured at 15°C into Solution ‘B’

with stirring at 1000 rpm to form a uniform emulsion (Gupta B.K. *et al*, 2009). Thereafter, it was allowed to attain room temperature and stirring was continued until residual acetone evaporated and smooth-wall, rigid and discrete microcapsules were formed. Microcapsules were collected by decantation and the product was washed with petroleum ether (40-60°C). Prepared microcapsules were dried at room temperature for 2 hours and after that they were dried in vacuum drier at about 60 mbar pressure for 4 hours at 40°C to obtain discrete microcapsules. The composition of all the twelve formulations prepared is given in table 2. The microcapsules were stored in a dessicator over fused calcium chloride till further studies.

PREFORMULATION STUDIES

The preformulation studies involves the study of physical and chemical properties of a drug alone and when combined with excipients' in order to choose what other ingredients (excipients') should be used in the preparation. Drug-polymer compatability studies ; For the studies FT-IR spectrophotometer, DSC (Differential Scanning Calorimetry) were used to find out any interaction between drug and polymers.

Physicochemical Characterization

(a) Appearance: Diclofenac Sodium is a white, crystalline and odourless powder.

(b) Melting Point: Melting point was determined by Melting Point Apparatus.

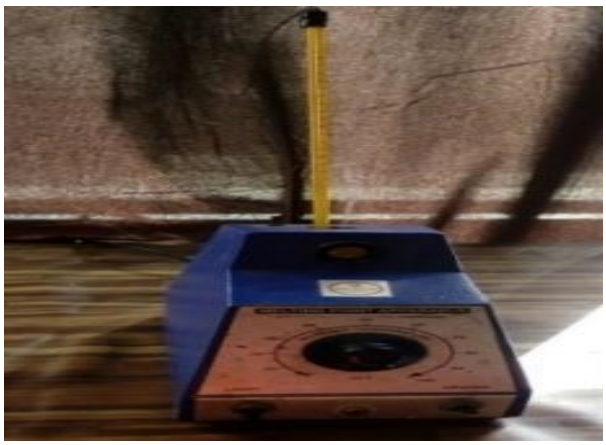


Fig. 1: Melting Point Apparatus.

(c) Partition coefficient

Partition coefficient provides a means of characterizing the lipophilic/hydrophilic nature of a drug. Partition coefficient of Diclofenac Sodium was determined at 37 + 0.5°C by taking n-octanol and water.

Identification of Drug

(a) Fourier Transformation Infrared Analysis

The Fourier Transformation Infrared Spectroscopy (FTIR) was performed in Fourier Transformation Infrared Spectrophotometer (FTIR Spectrophotometer Perkin-Elmer BX 11) by KBr pellet method in the range of 4000-500 cm-1 to confirm the authenticity of the drug Diclofenac Sodium.

(b) Differential Scanning Calorimetric Analysis

DSC thermogram of Diclofenac Sodium was recorded using Differential Scanning Calorimeter (Perkin-Elmer DSC-4000,USA) to confirm authenticity of drug sample. A small amount (2-5mg) of sample was sealed in the aluminium pan and heated in a temperature range 50-300°C at the heating rate of 10°C per minute in the presence of nitrogen atmosphere.

DRUG - EXCIPIENT INTERACTION STUDIES

(a) Fourier Transformation Infrared Analysis

FT-IR spectroscopy is a well-known method to identify the interaction between two functional groups. FT-IR spectroscopy of Diclofenac Sodium, Polymers (Eudragit® RS 100 and Eudragit® RL 100) and their physical mixture was performed. The interaction, if any, between drug and polymers was investigated by comparing the peaks of characteristic functional groups in the FT-IR spectra.

Fig. 2: FT-IR Spectrophotometer.

(b) Differential Scanning Calorimetric Analysis

DSC was used to characterize the physical state of the drug. The DSC thermogram of the drug, excipients' and the formulation exhibited peaks corresponding to their melting point, transition temperature. On the basis of change in the characteristic peak of the sample, drug-polymer interaction studies were done.

Table. 2: Formulation of Microcapsules of Diclofenac Sodium.

S.No.	Batch code	Drug (mg)	Eudragit® RS100 (mg)	Eudragit® RL100 (mg)	Acetone (ml)	Span 80 (%w/w)	Magnesium stearate (mg)	Stabilizer (Sodium alginate) (g)
1.	F1	100	300	250	20	1	80	0.05
2.	F2	100	350	300	20	1	80	0.1
3.	F3	100	400	350	20	1	80	0.15
4.	F4	100	450	400	20	1	80	0.2
5.	F5	100	500	450	20	1	80	0.25
6.	F6	100	550	500	20	1	80	0.3
7.	F7	100	600	550	20	1	80	0.35
8.	F8	100	650	600	20	1	80	0.4
9.	F9	100	700	650	20	1	80	0.45
10.	F10	100	750	700	20	1	80	0.5
11.	F11	100	800	750	20	1	80	0.55
12.	F12	100	850	800	20	1	80	0.6

CHARACTERIZATION OF MICROENCAPSULES

1) Particle Size Analysis

Particle size analysis of microcapsules was carried out by using optical microscope with 10x and 100x optical zoom. A minute quantity of microcapsules was dispersed in water and then spreaded on clean glass slide and average size of 100 microcapsules was determined for each batch.

2) Micromeritic studies

The flow properties of microcapsules were characterized in terms of Angle of repose,Carr's index,Hausner's ratio (Venkatesh Teja B *et al*,2012).

Table. 3: Micromeritic studies.

Flow Character	Angle of repose(°)	Carr's Index	Hausner's Ratio
Excellent	25-30	< 10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very Poor	56-65	32-27	1.46-1.59
Very,Very Poor	>66	>38	>1.60

Flow properties of powders were assessed by determining the angle of repose of the powders. The Carr's Index is an indication of the compressibility of a powder and the Hausner's Ratio is a number that is correlated to the flowability of a powder. Angle of repose more than 45° is an indication of poor flow properties while those with angle close to 25° corresponds to very good flow properties, a Carr's Index greater than 25 is considered to be an indication of poor flowability, and below 15,of good flowability. A Hausner's Ratio greater than 1.25 is considered to be an indication of poor flowability (Table 3).

The Hausner's ratio (H) and Carr's index of accurately weighed microcapsules were calculated according to the two equation-

Hausner's ratio (H) = DF/Do
Carr's index(%)= [(DF- Do)/DF] × 100
DF=Tapped density
Do=Bulk density

Angle of repose measured by using the fixed funnel method.
Angle of repose(Θ)= tan-1 (h/r)
h=Pile height
r=Base radius

3) Estimation of drug content

Drug content in microcapsules was estimated by using UV-Visible double beam spectrophotometer at 276nm. A quantity of microcapsules equivalent to 50 mg was powdered and transferred into a 100 ml volumetric flask. Sufficient amount of chloroform was added to produce 100ml, sonicated for 2-4 minutes until microcapsules were dissolved and filtered. Then 2 ml of the filtrate was diluted to 100 ml with phosphate buffer pH 7.4.

Drug content

$$\frac{\text{Amount of drug calculated from solution}}{\text{Weight of the formulation taken}} \times 100$$

Fig. 3: Probe Sonicator.

4) Encapsulation efficiency (E.E.)
The encapsulation efiiciency of the prepared microcapsules was calculated by using equation-

$$\textbf{E.E.} = \frac{\text{Amount of drug added - Amount of free drug}}{\text{Amount of drug added}} \times 100$$

5) Differential Scanning Calorimetric Analysis
The physical states of drug inside microcapsules was investigated by DSC. The DSC thermogram of optimized batch was obtained using Differential Scanning Calorimeter (perkin-Elmer, USA). The sample was sealed in aluminium pan and heated in range of 50-300°C at a heating rate of 10°C /min under nitrogen atmosphere.

6) Scanning Electron Microscopy
The morphology of Microcapsules was examined by Scanning Electron Microscopy Technique (SEM-Joel, JSM-6360).

7) X-Ray Powder Diffractometry
X-ray powder diffractometry was carried out to investigate the effect of microencapsulation process on crystallinity of drug. Powder X-RD patterns were recorded on PW 3710 diffractometer using a voltage of 40kV and a current of 30mA.The scanning rate employed was 50 min-1,over 50 to 40 diffraction angle (2Θ) range. The X-RD patterns of drug and selected formulation was recorded.

***In vitro* drug release studies**
The *in vitro* drug release studies were performed on microcapsules of Diclofenac Sodium using USP dissolution apparatus II (Paddle type) (stirring speed 100rpm, 0.1 N HCl and phosphate buffer pH 7.4, temperature (37+0.5°C). For 2 hours, study was performed in 0.1 N HCl and for next 10 hours study was performed in phosphate buffer pH 7.4. Accurately weighed amount of formulated microcapsules equivalent to 50 mg of drug was placed in muslin cloth, tied closely and was put in vessel containing 900 ml 0.1 N HCl / phosphate buffer pH 7.4. Sample aliquots of 5ml were withdrawn at specific intervals and replaced with equal volume of fresh 0.1 N HCl / phosphate buffer pH 7.4 solution to maintain sink conditions. After suitable dilution, samples were anlaysed by UV-Visible spectrophotometer at 276nm against suitable blank.

Drug release kinetics
The release kinetics was studied for various kinetic models such as zero order, first order, Higuchi and Korsmeyer-Peppas.[7]

To study the release kinetics of selected formulation, data obtained from *in vitro* drug release studies was plotted in various kinetic models :zero order as cumulative amount of drug released Vs time, first order as log cumulative percentage of drug remaining Vs time, Higuchi model as cumulative percentage of drug released Vs square root of time and Korsemeyer -Peppas as log of cumulative percentage drug release vs log time. The best fit model was confirmed by the value of correlation coefficient.

Zero Order Model
Drug dissolution from dosage forms that release the drug slowly can be represented by the equation.
$Q0-Qt = K0t$ (1)

Rearrangement of equation (1) yields
$Qt = Q0+ K0t$ (2)

Where Qt is the amount of drug dissolved in time t,
Q0 is the initial amount of drug in the solution (most times, Q0=0) and K0 is the zero order release constant expressed in units of concentration/time. To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as cumulative amount of drug Vs time.

First Order Model
The model has also been used to describe absorption and/or elimination of some drugs. The release of drug which follow first order kinetics can be expressed by the equation
$\log C = \log C0 - Kt/2.303$

Where C0 is the initial concentration of drug, K is the first order rate constant and t,is the time. The data obtained was plotted as log cumulative percentage of drug remaining Vs time which would yield a straight line with a slope of = K/2.303.

Higuchi Model
Graph was plotted between cumulative percentage of drug released Vs square root of time.
$Q=K\sqrt{t}$

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence drug release rate is proportional to the square root of time.

Korsmeyer Peppas Model

Korsmeyer derived a simple relationship which described drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug release data was fitted in Korsemeyer -Peppas model.

$Mt/M\infty=Ktn$

Where $Mt/M\infty$ is a fraction of drug released at time t, k is the release rate constant and n is the release exponent. Then value is used to characterize different release for cylindrical shaped matrices. For the case of cylindrical tablets, $0.45<n$ corresponds to fickian diffusion mechanism,$0.45<n<0.89$ to non-fickian transport, n = 0.89 to case(ii)(relaxational) transport, and n >0.89 to super case (iii) transport. To find out exponent n the portion of the release curve, where $Mt/M\infty < 0.6$ should only be used.To study the release kinetics, data obtained from *in vitro* drug release studies were plotted as log cumulative percentage drug release versus log time.

Stability studies

All the formulations were investigated for their stability profile by keeping them at 45 + 2°C and 75 + 5 % RH for 12 weeks. At the end of 12 weeks, they were analysed for any change in appearance, colour and drug content.

RESULTS AND DISCUSSION

Physicochemical Characterization

(a) Appearance

Diclofenac Sodium is white, crystalline and odourless powder.

(b) Solubility of Drug in different solvents

Diclofenac Sodium was freely soluble in methanol, ethanol, acetone, chloroform and sparingly soluble in water or in acetic acid. It is practically insoluble in ether (data not shown).

(c) Melting Point

The observed melting point of drug by using melting point apparatus was found to be in the range of 280-288°C.

(d) Partition Coefficient

The observed partition coefficient of drug was found to be log P = 2.27, it shows the drug is lipophilic in nature.

Identification of Drug

(a) Fourier Transformation Infrared Analysis

The FT-IR spectrum is shown in Fig.4.

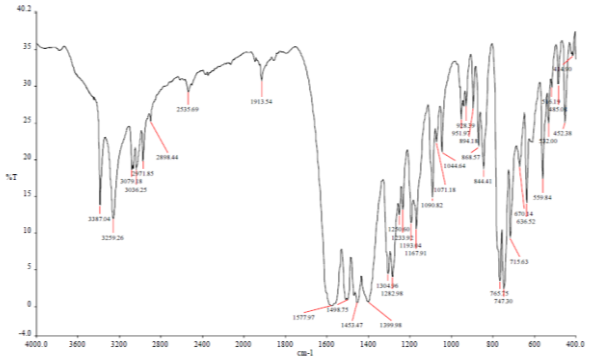


Fig. 4: FT-IR Spectrum of Diclofenac Sodium.

b) Differential Scanning Calorimetry Analysis

The endothermic peak with a peak maximum at 288.94°C indicated the melting point and crystalline anhydrous nature of the drug. The onset of melting of the drug was found to be at 283.38°C.

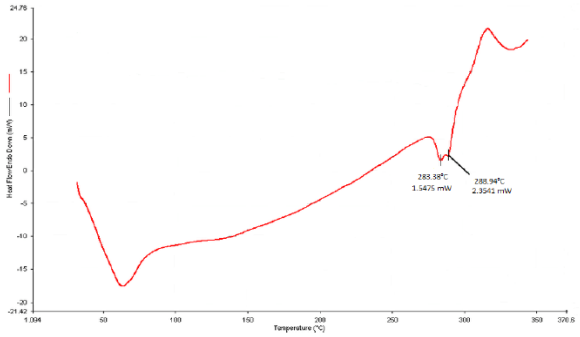


Fig. 5: DSC Thermogram of Diclofenac Sodium.

DRUG – EXCIPIENTS' INTERACTION STUDIES

The compatibility of drug with excipients' was studied using techniques like FT-IR and DSC to find any kind of destructive interaction between drug and polymers used in the study.

(a) Fourier Transformation Infrared Analysis.

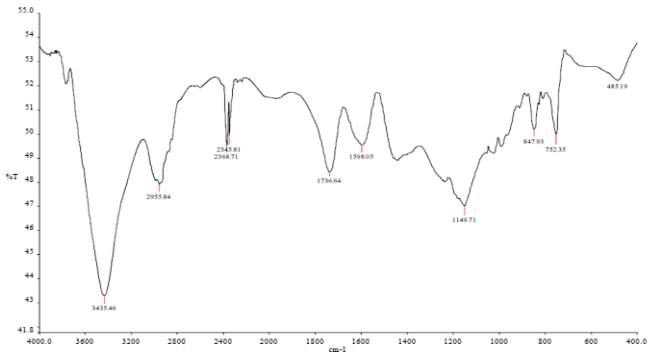


Fig. 6: FT-IR Spectrum of Eudragit® RS 100.

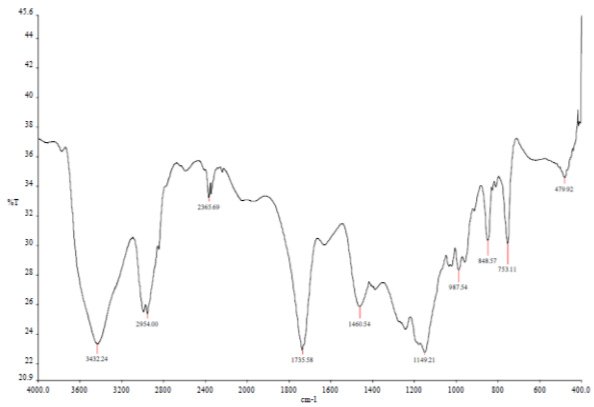


Fig. 7: FT-IR spectrum of Eudragit® RL 100.

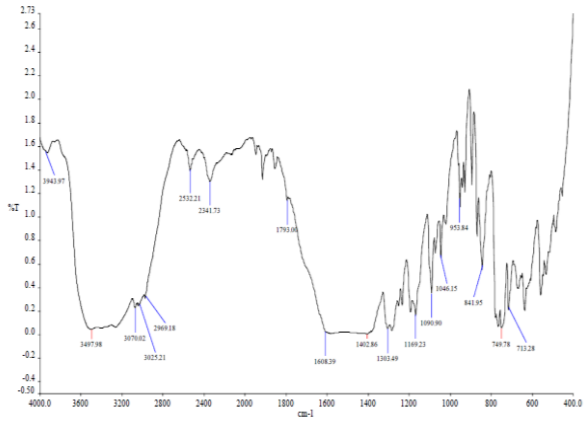


Fig. 8: FT-IR spectrum of physical mixture of Diclofenac Sodium, Eudragit® RS 100 and Eudragit® RL 100.

The characteristic peaks of Diclofenac Sodium, Eudragit® RS 100 and Eudragit® RL 100 were present in the physical mixture, thus indicating that there was no significant evidence of chemical interaction between drug and polymers, which confirms the stability of drug in presence of Eudragit® RS 100 and Eudragit® RL 100.

(b) Differential Scanning Calorimetry Analysis

The DSC thermogram of pure drug Diclofenac Sodium, physical mixture of Eudragit® RS 100 and Eudragit® RL 100 and selected batch of microcapsules of Diclofenac Sodium are shown in Fig. 9, Fig.10.The DSC thermogram of physical mixture suggested that there were no appearance of new peaks or disappearance of existing peak in the curve, the melting point shows slight deviation from respective pure samples. Hence it was concluded that the drug and excipients' did not undergo any considerable interaction.

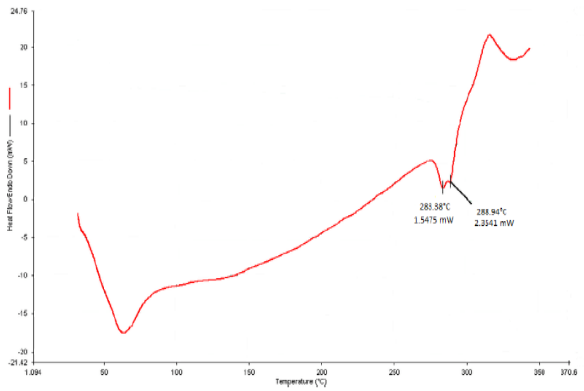


Fig. 9: DSC thermogram of Diclofenac Sodium.

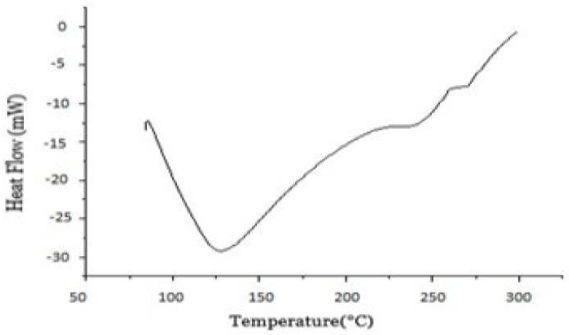


Fig. 10: DSC thermogram of physical mixture of drug and Eudragit® RS 100 and Eudragit® RL 100.

CHARACTERIZATION OF MICROCAPSULES OF DICLOFENAC SODIUM

The Microcapsules of Diclofenac Sodium were evaluated for various parameters as described below.

Micromeritic Properties

The particle size, Carr's index, Hausner's ratio and angle of repose of different batches of Microcapsules of Diclofenac Sodium are shown in table 4

Table. 4: Particle size, Carr's index, Hausner's ratio and Angle of repose of different formulations of Microcapsules of Diclofenac Sodium.

Formulation	Particle size (Mean ± S.D.) (µm)	Carr's index (%) (Mean ± S.D.)	Hausner's ratio (Mean ± S.D.)	Angle of repose (°) (Mean ± S.D.)
F1	203.49 ± 0.79	13.6 ± 0.25	1.169 ± 0.013	15.6 ± 0.25
F2	222.60 ± 6.80	9.3 ± 0.05	1.114 ± 0.019	19.9 ± 0.11
F3	258.78 ± 7.57	14.5 ± 0.15	1.168 ± 0.010	20.8 ± 0.74
F4	343.70 ± 7.26	11.3 ± 0.25	1.128 ± 0.009	22.8 ± 0.61
F5	361.29 ± 1.47	6.6 ± 0.2	1.081 ± 0.014	24 ± 0.46
F6	366.54 ± 1.05	10.6 ± 0.20	1.134 ± 0.022	24.7 ± 0.85
F7	390.26 ± 8.69	12.5 ± 0.30	1.154 ± 0.020	25.7 ± 0.65
F8	396.94 ± 4.13	9.6 ± 0.26	1.119 ± 0.014	27.3 ± 0.72
F9	412.29 ± 0.31	7.5 ± 0.05	1.136 ± 0.087	26.8 ± 0.88
F10	433.52 ± 9.65	8.4 ± 0.15	1.132 ± 0.054	27.3 ± 0.55
F11	463.56 ± 28.3	11.6 ± 0.26	1.131 ± 0.011	28.6 ± 0.56
F12	495.67 ± 21.9	14.2 ± 0.25	1.171 ± 0.013	28.9 ± 0.46

S.D.(Standard Deviation)
n=100 for column 1,n=3 for column 2 to 4.

The average mean particle size of prepared formulations F1 to F12 was found to be in the range of 203.49-495.67 µm. From the above results, it was observed that the particle size increased with increase in the amount of Eudragit® RS100 and Eudragit® RL100. The arithmetic mean particle size of the formulations was determined by the optical microscope fitted with an ocular micrometer and stage micrometer. The Carr's Index, Hausner's Ratio and Angle of Repose of the prepared formulations F1-F12 was found to be very close to the reported values.

Drug Encapsulation efficiency

The Percentage Encapsulation Efficiency of Drug in the microcapsules ranged from 79.60-96.37% which indicated that increase in amount of Eudragit® RS100 and Eudragit® RL100 also increased the encapsulation efficiency of drug (Table 5).

Table. 5: The Encapsulation Efficiency data of different formulations.

Formulations	Encapsulation Efficiency (%(Mean+ S.D.)
F1	79.60+0.03
F2	83.27+ 0.17
F3	84.52+ 0.08
F4	85.63+0.42
F5	86.93+0.02
F6	90.12 + 0.22
F7	91.77+ 0.07
F8	94.36+0.05
F9	95.66+0.06
F10	96.37+0.07
F11	95.97+0.02
F12	96.15+0.08

S.D.(Standard Deviation),n=3.

Drug Content

The drug content of the formulations generally increased with the increase in polymer concentration.

Table. 6: The Drug Content data of different formulations.

Formulations	Drug Content (% (Mean+ S.D.)
F1	59.21+0.07
F2	66.54+0.35
F3	69.04+0.17
F4	71.27+0.84
F5	73.86+0.05
F6	80.25+0.45
F7	83.54+0.15
F8	88.73+0.09
F9	91.33+0.12
F10	92.75+0.13
F11	91.95+0.05
F12	92.3+0.16

S.D.(Standard Deviation), n=3.

***In vitro* drug release studies**

The drug release studies were carried out in 0.1 N HCL (2 hours) and in phosphate buffer pH 7.4 (10 hours). All the formulations showed less than 6 % drug release in 0.1 N HCL. However, the drug release in phosphate buffer pH 7.4 was found to be in the range from 11.82-88.07%. The lesser amount of drug release in acidic medium may be attributed to the synergistic effect of the polymers used namely (Eudragit® RS 100 and Eudragit® RL 100) and sodium alginate. The formulation F10 showed the highest drug release of about 88%.

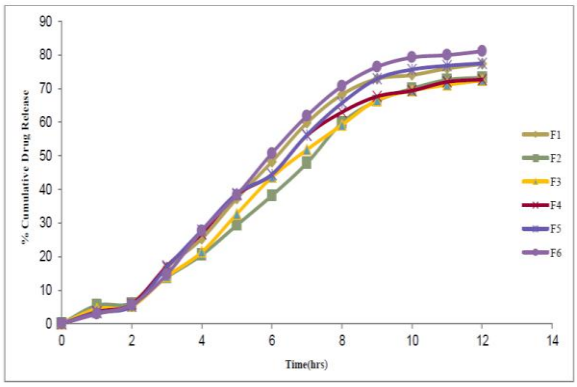


Fig.11: Drug Release Profiles of formulations F1-F6.

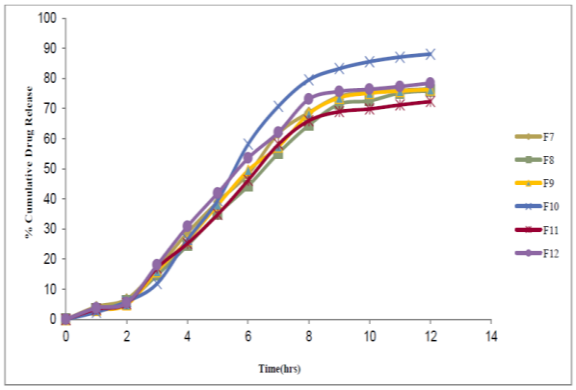


Fig.12: Drug Release Profiles of formulations F7-F12.

CHARACTERIZATION OF SELECTED BATCH
Differential Scanning Calorimetric Analysis.

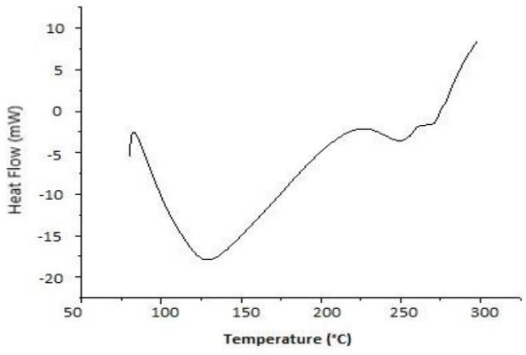
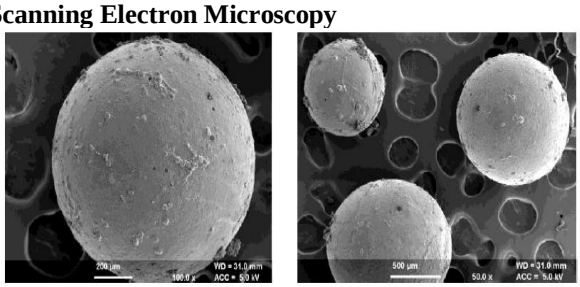
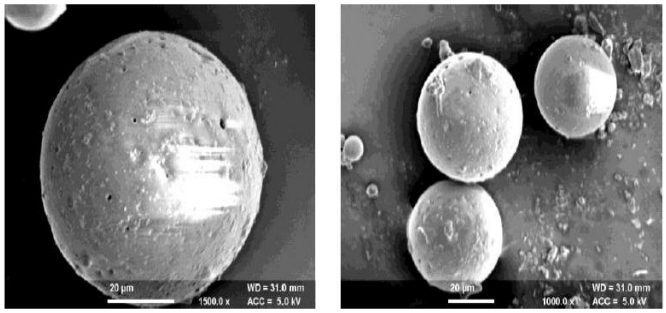


Fig. 13: DSC thermogram of selected formulation (F10).

Scanning Electron Microscopy



(a)



(b)

Fig. 14: Scanning Electron Microscopy images of selected batch (F10.

X-ray powder Diffractometry (X-RD)

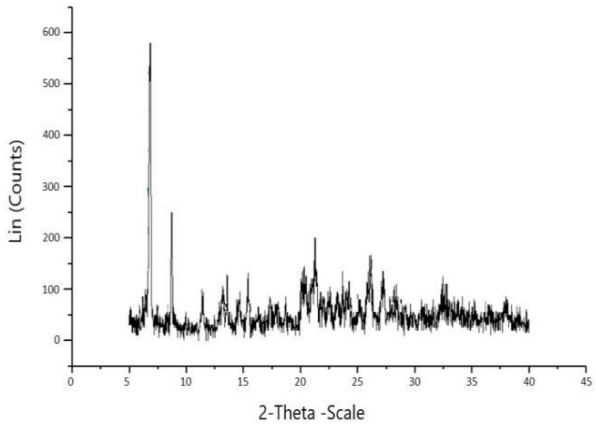


Fig. 15: X-RD Powder Diffraction spectrum of Diclofenac Sodium.

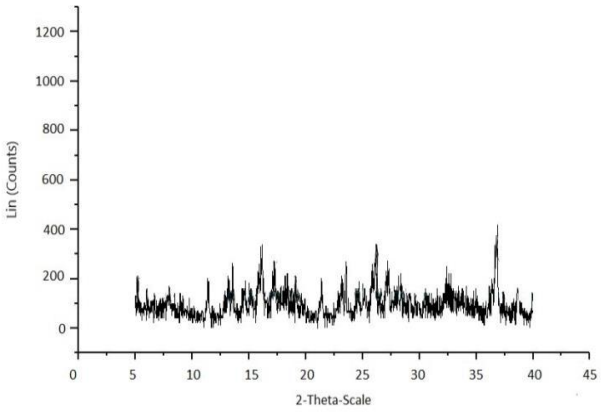


Fig. 16: X-RD Powder Diffraction spectrum of selected formulation.

The X-ray powder diffractometry (X-RD) of the drug showed that the drug is crystalline in nature and on microencapsulation of Diclofenac sodium with Eudragit® RS-100 and Eudragit® RL-100, crystallinity of drug decreases.

***In vitro* drug release profile of selected batch**

Table 7: % Cumulative Drug Release data of selected formulation F10.

S.No.	Time(Hours)	% Cumulative Drug Release (Mean + S.D.)
0	0	0 + 0
1	1	2.37+0.24
2	2	5.87 +0.42
3	3	11.82 +0.80
4	4	26.39 +0.67
5	5	39.47 +0.48
6	6	58.11 +0.80
7	7	70.74 +0.56
8	8	79.49+0.47
9	9	83.22+0.31
10	10	85.55+0.52
11	11	87.08+0.25
12	12	88.07+0.30

S.D.(Standard Deviation), n=3.

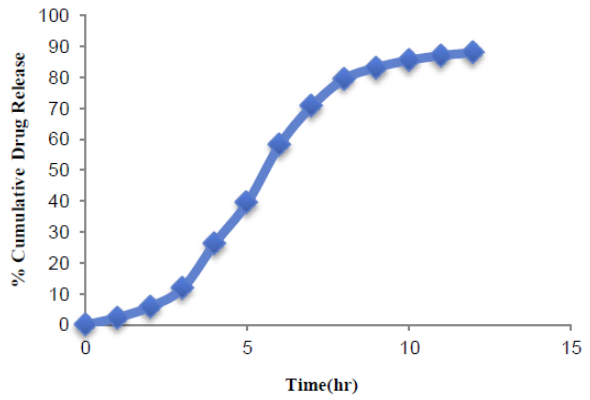


Fig. 17: *In vitro* drug release profile of selected batch F10.

***In vitro* drug release kinetics**

In vitro drug release kinetics data of selected formulation (F10) is given below

Zero order

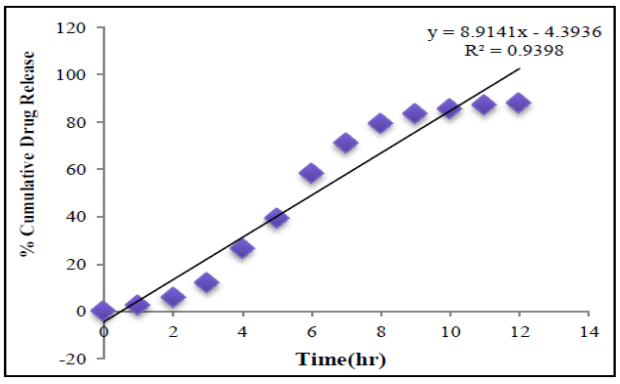


Fig. 18: Zero order graph of selected batch F10 First order.

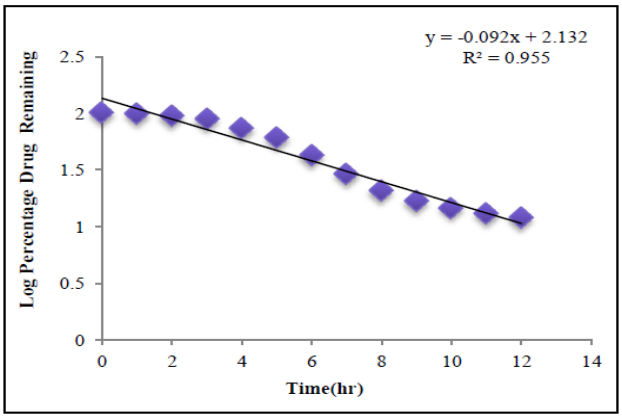


Fig. 19: First order graph of selected batch F10.

Higuchi Model.

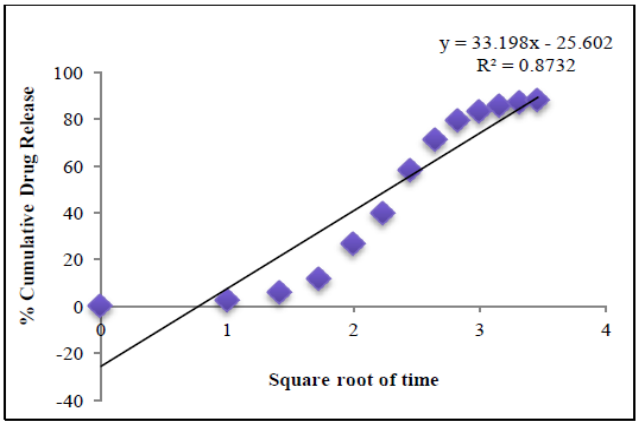


Fig. 20: Higuchi Model graph of selected batch F10.

Korsmeyer Peppas Model

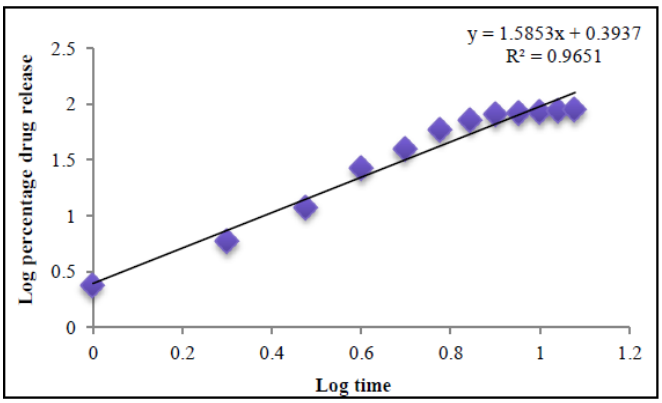


Fig.21:Korsmeyer-Peppas Model graph of selected batch F10.

Table. 8: Drug Release Kinetic equation parameters of selected batch (F10).

Formulation Name	Zero order		First order		Higuchi		Korsmeyer-Peppas	
	R^2	K_0	R^2	K_0	R^2	K_0	R^2	K_0
F 10	0.939	8.914	0.955	-0.092	0.865	33.19	0.965	1.585

Stability study

Table. 9: Stability Study Data of different formulations

Formulation	Amount of the drug (%) present in the formulation after 12 weeks (Mean+ S.D.)
	45 + 2°C, 75+ 5% (RH)
F1	54.40+0.51
F2	63.58+0.09
F3	67.04+0.32
F4	68.17+0.29
F5	72.37+0.19
F6	77.21+0.05
F7	79.72+0.33
F8	86.08+0.07
F9	90.14+0.05
F10	91.07+0.11
F11	91.24+0.14
F12	91.82+0.13

S.D.(Standard Deviation),n=3

Drug stability is a key quality attribute considered during product development process. The percentage of the drug content of all the microcapsules during stability studies at temperature 45 + 2°C and 75+ 5 % (RH) for 12 weeks was found to be in the range of 54.40% to 91.82% . The percentage drug content of the formulations after exposure to experimental conditions revealed that the formulations were stable.

CONCLUSION

The drugs choosen for microencapsulation mostly belongs to BCS class I and BCS class II. Class II comprises of drugs that have low solubility and high permeability (Shreya Mukherji *et al*,2015). These drugs get easily eliminated from the site of absorption as the dissolution rate is slows.This may result in the reduced bioavailability. Thus, to enhance the bioavailability of these drugs, they can be microencapsulated with release retarding polymers.

Diclofenac Sodium is BCS class II drug (High permeability, Low water solubility), low water solubility is the limiting step for absorption and bioavailability. It possesses narrow therapeutic index due to its short biological half-life and it gets eliminated from plasma compartments within few hours, so frequent administration is necessary to maintain its therapeutic concentration. Exposure of stomach to high level of Diclofenac Sodium can cause gastrointestinal damage such as ulceration or bleeding, it requires immediate termination of treatment. So, the present investigation was aimed developing sustained release microcapsules of Diclofenac Sodium for decreasing the dosing frequency, resulting in less frequent dosing, for avoiding gastric irritation and increasing its hydrophilicity.

The identification and characterization studies of Diclofenac Sodium were carried out with the help of UV visible spectrophotometry. FTIR spectrophotometry, DSC analysis, XRD diffractometry and the drug found to be pure and authentic. Drug-excipient interaction studies were carried out to determine any interaction between drug and polymer, and no interaction was observed. The microcapsules of Diclofenac Sodium were prepared by solvent evaporation technique by varying the concentration of Eudragit RS100, Eudragit RL100 polymer and sodium alginate. The microcapsules of Diclofenac Sodium were characterized by particle size distribution, micromeritic properties, drug content, encapsulation efficiency, crystallography and *in vitro* drug release.[22]

The effect of formulation variables such as Eudragit® RS 100, Eudragit® RL 100 and effect of sodium alginate were investigated.

The solvent-evaporation method using Eudragit polymers at various levels was found to be effective for the formation of Diclofenac Sodium microcapsules. It was found that formulation F10 was satisfactory in terms of excellent micromeritic properties, encapsulation efficiency (96.37%) and *in vitro* drug release upto (88.07 %) in a sustained manner. So from the results, it could be concluded that concentration of polymers affected the evaluation parameters. The particle size was found to be in the range of 203.49 µm and 495.67µm. The encapsulation efficiency of microcapsules of Diclofenac Sodium ranged from 79.6-96.37 %. The *in vitro* drug release studies were carried out for 2 hours in 0.1 N HCL and for next 10 hours studies were carried out in phosphate buffer pH 7.4. The extent of drug release was found in the range 72.3-88.07 %. The data obtained from *in vitro* release profile of Diclofenac Sodium indicate that all the batches of microcapsules showed controlled and prolonged drug release and spread over an extended period of time. It was observed that the drug release from microcapsules decreased with an increase in the amount of polymeric material (Eudragit® RS 100 & Eudragit® RL 100) in the microcapsules.

The kinetics of release profile of the drug from Microcapsules of Diclofenac Sodium was found to follow Korsmeyer-Peppas model. This indicated that the drug release occurred by a combination of diffusion as well as erosion mechanism. SEM Images of selected formulation batch revealed that all microcapsules formulations were almost spherical in shape and had a smooth surface.

It was observed that microcapsules of Diclofenac Sodium showed promising results. The potential use of the formulations for a more effective management of inflammation and in pain may be further explored with the help of long term pharmacokinetic and pharmacodynamic studies.

ACKNOWLEDGEMENT

We will like to acknowledge the sincere efforts of our research scholars Sunny Rupana, Surbhi Rohilla, and Smridhi whose contribution helped us in our work.

REFERENCES

1. Banker GS and Rhodes CT. (Modern Pharmaceutics).In Pharma Publication, 2002; 121: 501-527.
2. Benita Simon. Microencapsulation methods and applications. Published by CRC press, 2014; 7(76): 1-9, 43-50, 155-159, 451.
3. Deasy Patrick B.Microencapsulation and releated processes. Marcel Dekker, 2007; 20(7):1-11, 21-27, 289-302.
4. Ehsaneh Jafari. (Preparation, characterization and dissolution of solid dispersion of diclofenac sodium using Eudragit E-100). Journal of applied pharmaceutical science, 2013; 3(8): 167-170.
5. Evonik Nutrition & Care GmbH, Pharma Polymers & Services, Kirschenallee, Germany.
6. Gupta B.K.,Pal R, Chakraborty Manas, Debnath R. (Design, evaluation and optimization of microcapsules of leflunomide with Eudragit® RL 100 and Eudragit® RL 100 by solvent evaporation technique). Asian Journal of Pharmaceutics, 2009.
7. Hina Kouser Shaikh, R.V. Kshirsagar and S.G.Patil. (Mathematical models for drug release characterization). World journal of pharmaceutical research, 2015; 4(4): 324-338.
8. Joel GH and Lee EL. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 11th edition, 2011 ; 1415.
9. Kulkarni AS and Gaja JB. (Formulation and evaluation of liquisolid compacts of diclofenac sodium). J Pharm Sci Technol, 2010; 64(3): 222-32.
10. Mahmood Ahmad, Asadullah Madni and Muhammad Usman. (Pharmaceutical Microencapsulation Technology for development of controlled release drug delivery systems).World academy of science, engineering and technology, 2011; 384-387.
11. Masheer Ahmed Khan.(Enhancement of solubility of poorly water soluble drug diclofenac sodium by mixed solvency approach). Int J of Research and Development in Pharmacy and Life Sciences, 2015; 4(6): 1835-1837.
12. Nitika Agnihotri, Ravinesh Mishra, Chirag Goda and Manu Arora. (Microencapsulation-A Novel Approach in Drug Delivery), Indo Global Journal of Pharmaceutical Sciences, 2015; 2(1): 1-20.
13. Shreya Mukherji and Vivek Nalawade. (Microencapsulation: A review on polymers and correlation with BCS classification of drugs), Int J Pharm Bio Sci., 2015; 6(3): 305 – 317.
14. Venkatesh Teja B, Bharath S, Deveswaran R, Basavaraj BV and Madhavan V. (Modified multiple emulsion technique for the microencapsulation of Diclofenac Sodium using olibanum resin as a polymer), International journal of pharmaceutical and chemical sciences, 2012; 1(2): 508-513.
15. Read More: http://pubmed.com/doi.org:10.1080/02652040210000 22734.
16. https://doi.org/10.1016/S0378-5173(01)00573-7.
17. https://doi.org/10.1016/S0168-3659(97)00203-4.
18. https://doi.org/10.1016/j.ipharm.2008.09.006.
19. https://www.drugs.com/diclofenac.html.