EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 8
279-292
Year: 2018

FORMULATION AND OPTIMIZATION OF SUSTAIN RELEASE INDOMETHACIN CAPSULE

[1*]Preeti Khulbe and [2]Birendra Srivastava

[1]M Pharm., Asst Professor, [2]PhD, Director, Professor
School of Pharmaceutical Sciences, Jaipur National University, Jaipur (Rajasthan).

***Corresponding Author: Preeti Khulbe**
M. Pharm., Asst Professor, School of Pharmaceutical Sciences, Jaipur National University, Jaipur (Rajasthan).

Article Received on 22/05/2018 **Article Revised on 11/06/2018** **Article Accepted on 02/07/2018**

ABSTRACT
Indomethacin is a nonsteroidal anti-inflammatory drug (NSAID) which is commonly used as prescription drug to reduce fever, stiffness and pain. In this Indomethacin is used as model drugs. Different formulations were prepared by using optimization technique. Wet granulation method was used for making Indomethacin sustain release granules. In this method rate retarding polymers (Guar gum, Xanthan gum & ethyl cellulose) were added in the formula. *Ex vivo* permeation study was performed in selected optimized batch. Non-everted intestinal sac method was used to determine *Ex-vivo* permeation study. After optimization statistical analysis of optimized formulations were performed on the bases of full factorial 2^3 design by using response surface plot, ANOVA and order of reaction. Prepared optimized formulation was compared with marketed formulation. The prepared optimized capsule is having 99.84% drug release from sustained release indomethacin upto 12 hrs.

KEYWORDS: Indomethacin, sustained release, *Ex vivo,* Xanthan gum, Guar gum.

INTRODUCTION

NSAIDs are used for treating the acute or chronic conditions of pain and inflammation. Indomethacin is a nonsteroidal anti-inflammatory drug (NSAID) which is commonly used as prescription drug to reduce fever, stiffness and pain. It mainly inhibits the production of prostaglandins and molecules which causes these type of symptoms. Indomethacin is a cyclooxygenase or COX also known as prostaglandin growth hormone synthase inhibitor which acts on both prostaglandin growth hormone synthase 1 as well as 2 (COX-1 & -2).[1] Indomethacin is a NSAIDs which is normally used for the symptomatic relief from following conditions: Arthritis, Mild-to-moderate pain because of inflammation, Low back pain, Inflammatory arthropathies (ankylosing spondylitis, psoriatic arthritis, reactive arthritis), Headache, Migraine, Tennis elbow, menstrual pain, Postoperative pain, Metastatic bone pain, Muscle stiffness & pain due to Parkinson's disease, Renal colic, Pyrexia (fever), Ileus.[2]

MATERIAL AND METHOD

Material

Methods

Pre-formulation studies

Pre-formulation studies focus on those physiochemical properties of the compounds that affect the drug performance and development of an efficacious dosage form. A thorough understanding of these properties, ultimately provide a rationale for formulation design. The data outcome of these studies elects many of the succeeding procedures and methods in the development of formulation. Drug identification test and drug excipient compatibility studies were done in this phase to provide a useful support in development of dosage forms. During pre-formulation stage organoleptic properties, melting point determination, micromaretic properties, particle size distribution and powder flow properties were determined using reported methods.[3]

Compatibility studies

Compatibility testing was carried out using binary mixture compatibility testing approach.[4] Briefly, the drug and excipients were mixed separately at 1:1 ratio and kept in a clean and dry glass vial. The sample containing glass vial was placed in a stability chamber (TP 200S, Thermolab, Mumbai, India) at 40±2°C and 75±5% RH for a period of 6 months. The samples were analyzed at 0, 3 and 6 months as per ICH guidelines.[5] The samples were analyzed on the basis of general appearance and IR spectra.

Solubility analysis

Determination of solubility

The solubility of pure drug was determined using shake flask method by preparing supersaturated solution of drug with water, ethanol and acetone.[6] The samples were analyzed using UV-spectrophotometer (UV 3000$^+$, LabIndia, Mumbai, India) at 256 nm after suitable dilutions (10).

Determination of partition coefficient

Partition-coefficient is the ratio of compound concentrations in a mixture of two immiscible phases at equilibrium. Shake-flask method was used for the determination of partition coefficient.[7] Briefly, 10 mg drug was mixed with 20 ml of octanol and water in a separating funnel and shaken for about half an hour. The separating funnel was kept for 24 h and concentration of solute was measured in each solvent using UV-spectrophotometer (UV 3000+, Lab India Instruments, Mumbai, India) at 256 nm.

$$\text{Partition Coefficient } (K_{o/w}) = \frac{\text{Concentration in oil}}{\text{Concentration in water}}$$

$$\text{Log } (P_{o/w}) = \log \frac{\text{Concentration in oil}}{\text{Concentration in water}}$$

Indomethacin SR Granulation

For indomethacin sustained release granules also the same wet granulation method was used.[8] In this case for sustain release of indomethacin polymers or sustain release excipients were added in the formula.

All the ingredients were weighed and sieved according to formula (Table 1) through sieve # 40. Mix all the sieved ingredients with the help of plastic polybag except PVPK-30, talc and magnesium stearate. Binding solution of PVPK-30 was then added into the mixed ingredients, and dough was formed. Then the dough was passed with the sieve # 10 to form desired size of granules. The prepared granules were then dried in oven for approximately 1 hrs at 60°C. then the dried granules were passed through sieve # 20 and mixed with talc and magnesium stearate. Finally, prepared granules were evaluated and stored in the air tight polybag.

Table 1: Formulation of SR Indomethacin trial batches.

Ingredients	Formulation Code: Quantity per capsule (mg)							
	IN-1	IN -2	IN -3	IN -4	IN -5	IN -6	IN -7	IN -8
Indomethacin	**75**	**75**	**75**	**75**	**75**	**75**	**75**	**75**
Xanthan Gum	6	15	10	7	10	27	-	-
Guar Gum	6	11	6	8	10	-	-	9
Ethyl cellulose	25	11	11	7	-	-	27	27
PVPK-30	9	9	9	4.5	4.5	9	9	9
Water	qs.	qs.	qs.	qs.	qs.	qs.	qs.	qs.
Lactose	41	41	51	60.5	62.5	51	51	44
Magnesium stearate	10	10	10	10	10	10	10	10
Talc	8	8	8	8	8	8	8	8
Total	**180**	**180**	**180**	**180**	**180**	**180**	**180**	**180**

IN-8 formulation was selected for optimization.

Optimization of Indomethacin

Full factorial 2^3 design[9] was used on selected formulation (IN-8). Amount of ethyl cellulose (15% & 20%) (X_1), amount of PVPK-30 (3.5% &5%) (X_2), and amount of guar gum (5% & 10%) (X_3) were used as independent variable. Coded value for 2 levels were -1, +1. Total 8 possible outcomes were prepared (Table 2). The percentage drug release was selected as dependent variable.

The optimization batches were also prepared by same procedure as trial batches.

Table 2: - Formulations of SR Indomethacin optimized batch.

Ingredients	Formulation Code: Quantity per capsule (mg)							
	OIN-1	OIN-2	OIN-3	OIN-4	OIN-5	OIN-6	OIN-7	OIN-8
Indomethacin	**75**	**75**	**75**	**75**	**75**	**75**	**75**	**75**
Ethyl cellulose*	27	27	27	27	36	36	36	36
PVPK-30*	9	9	6.3	6.3	9	9	6.3	6.3
Guar Gum*	9	18	9	18	9	18	9	18
Water	qs	qs	qs	qs	qs	qs	qs	qs
Lactose	44	33	44.7	35.7	33	24	35.7	26.7
Magnesium stearate	10	10	10	10	10	10	10	10
Talc	8	8	8	8	8	8	8	8
Total	**180**	**180**	**180**	**180**	**180**	**180**	**180**	**180**

Evaluation of prepared granules

Flow Properties

Flow properties of prepared granules are very useful in formulation development. Changes in particles size, and shape are generally very important an increase in crystal size or a more uniform shape will lead to a small angle of repose and a smaller Carr's index. In this bulk density, tapped density, angle of repose, compressibility index was determined.[10]

Drug Release (Dissolution Test)

USP type one dissolution test apparatus was used. [11] A single capsule was placed in a small wire mesh basket attached to the bottom of the shaft connected to a variable speed motor. The basket was immersed in a dissolution medium contained in a flask. The flask was cylindrical with hemispherical bottom. The flask was maintained at 37±0.5 ^{o}C by a constant temperature bath. The motor was adjusted to turn at the specified speed and sample of the fluid were withdrawn at intervals to determine the amount of drug in solutions.

Drug Release (Dissolution Test) on PSS

Apparatus: USP type 1 (basket type)
RPM: 100
Temp: 37°C
Time: 12 hrs
Volume of dissolution medium: 750ml of 0.1N HCl for 2 hrs then 250 ml of 0.2M tricalcium phosphate was added)
Final pH- 6.8
number of samples: 09.

***Ex vivo* permeation study**

Ex vivo permeation study was performed in selected optimized batch. Non-everted intestinal sac method[12] was used for this study. firstly, the Krebs ringer bicarbonate buffer solution was prepared according to the formula. Chicken intestine was procured from a slaughter house and small intestine was taken for the study. The lumen was carefully cleared from mucus by rinsing with pH 6.8 buffer solution (Krebs–Ringer solution: Table 3). An intestinal segment of the first 6-cm length was removed and transferred to oxygenated Krebs – Ringer solution. It was washed thoroughly with Krebs–Ringer solution.

The intestinal segment of about 6 cm in length were tied at one end and the sacs were filled with 5ml of kerbs-Ringer Bicarbonate buffer containing suspension of optimized formulation, then the other end was ligated carefully. The non-everted sac was submerged in a conical flask containing 100ml of kerbs-Ringer Bicarbonate buffer with maintained temp 37°C by heating mental (Fig 1).

The samples were then collected in different time interval; the equivalent fresh KR buffer was added to solution at the time of sampling. Each experiment was performed six times and proper dilutions of sample were done with KR buffer solutions and absorbance was measured using UV Spectrophotometry. Same experiment was repeated with marketed formulation.

Table no 3: composition of Krebs ringer bicarbonate solution.

Composition	Quantity (gm/L)
NaCl	7.0
KCl	0.06
$CaCl_2$	0.09
$MgSO_4.7H_2O$	0.16
$NaHCO_3$	2.3
KH_2PO_4	0.16
Glucose	1.8

Fig 1: Ex vivo study apparatus,

Evaluation of prepared formulation

General Appearance

The general appearance of a capsule, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and capsule to capsule uniformity.

Weight variation test

20 capsules were taken at random and weighed. Their average weight was calculated, then each capsule was weighed individually and their weight was noted.[13]

Disintegration test

For performing disintegration test on capsules the tablet disintegration test apparatus is used but the guiding disc may not be used except that the capsules float on top of the water. One capsule was placed in each tube which were then suspended in the beaker to move up and down for 30 minutes. The capsules pass the test if no residue of drug or other than fragments of shell remains on No. 10 mesh screen of the tubes.

Dissolution test

Dissolution procedure was same as follow in the dissolution of granules. In this case first 500 ml dissolution medium (as in case of PSS IR Formulation) was used after 30 min the dissolution medium was made upto 750 ml with 0.1 N HCl. Then it was again made upto 900 after 2 hrs with250 ml of 0.2M tricalcium phosphate. Sampling time was upto 12 hrs.[14]

Statistical Analysis

Statistical analysis of the optimization batches (OIN1-OIN8) was carried out on the bases of full factorial design and response surface plot, two-way ANOVA, and order of reaction. Statistical analysis was carried out using Design Expert 8.0.5.2 software (Stat-Ease, Inc., Minneapolis, Minnesota). The p value of <0.05 was considered statistically significant. To select the optimum formulation, various mathematical models such as zero order and first order were used to describe the kinetics of drug release.

Mathematical model

In mathematical model zero order, first order, Higuchi and Korsmeyer peppas model was determined for optimized formulation.[15]

RESULT AND DISCUSSION

Preformulation studies

Organoleptic properties

Table 4: Organoleptic properties of indomethacin.

Drug	Colour	Odour
Indomethacin	Pale yellow crystalline powder	Odourless

Discussion: On the bases of comparison of organoleptic properties between literature and observation it can be concluded that the drug is Indomethacin.

Melting point determination

Table 5: Melting point of indomethacin.

S. No.	Drug	Temperature(°C) (Drug starts melting)	Temperature (°C) (Drug completely melts)	Melting Point (°C)
1	Indomethacin	158	160	158-160
2	Indomethacin	159	160	
3	Indomethacin	158	160	

Discussion

On the bases of comparison of melting point between literature (158-162°C) and observation (158-160°C) it can be concluded that the drug is indomethacin.

Micromaretic Properties
Particle Size Distribution

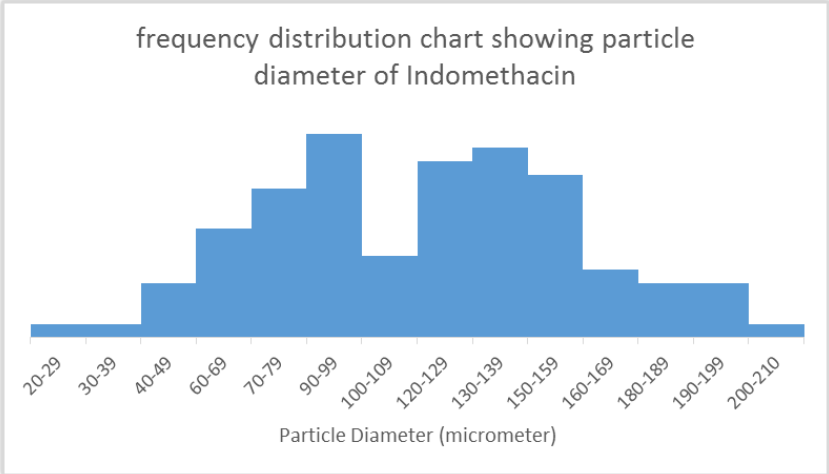


Fig 2: Particle size distribution of indomethacin.

Discussion

On the bases of observations, it can be concluded that the particles of given indomethacin were found to be in the range of 20 µm to 210 µm. The average size of particles was found to be 112.5 µm (calculated by taking arithmetic mean).

Flow Properties

Table 6: Flow properties of indomethacin.

S.No.	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Angle of Repose (Degree)	Compressibility Index (%)
1	0.462	0.769	30.45	39.92
2	0.476	0.793	25.22	39.97
3	0.526	0.831	26.15	36.70

Discussion

On the bases observations the average bulk density of the given drug was found to be 0.488 gm/ml. The observed average tapped density of the given drug was found to be 0.797 gm/ml. Average angle of repose of the given drug was found to be 27.27° and the average the compressibility index of the given drug was found to be 38.86%.

Solubility Analysis
Calibration Curve

Table 7: Concentration and absorbance of indomethacin in ethanol & phosphate buffer 6.8 pH.

Ethanol (soluble in ethanol)
λ max is 260 nm.

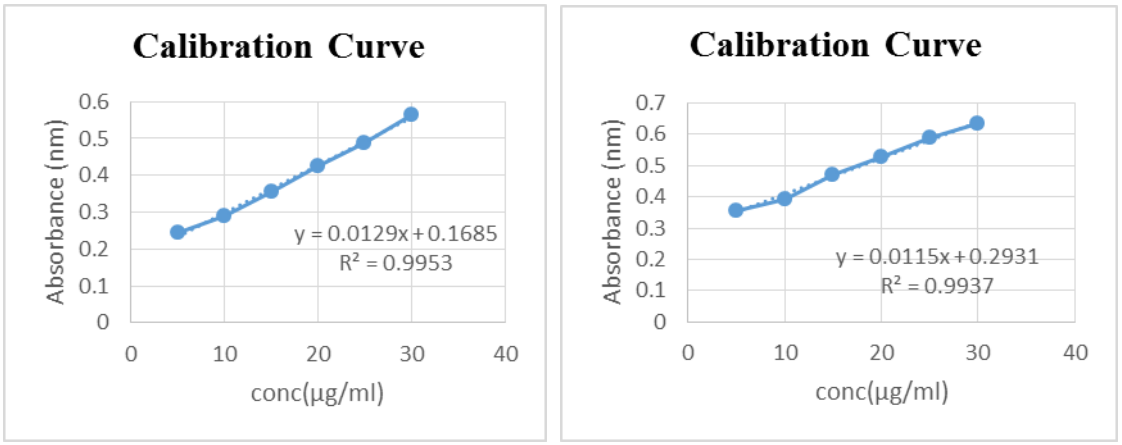
Concentration (µg/ml)	Absorbance (nm)
5	0.245
10	0.289
15	0.357
20	0.426
25	0.487
30	0.565

(A)

Phosphate buffer 6.8 pH
λ max is 256 nm

Concentration (µg/ml)	Absorbance (nm)
5	0.356
10	0.394
15	0.471
20	0.529
25	0.587
30	0.632

(B)



(A) **(B)**

Fig 3: Calibration curve of indomethacin in ethanol (A) & phosphate buffer 6.8 PH (B).

Solubility Profile

Table 8: Solubility profile of indomethacin.

S. No.	Solvent	Solubility
1	Water	Practically insoluble
2	Acetone	Soluble
3	Ethanol	Soluble

Discussion

On the bases of observations, it can be concluded that the indomethacin was a water insoluble drug.

Partition Coefficient

Table 9: Partition coefficient of indomethacin.

S. No.	Partition Coefficient
1	3.62
2	3.57
3	3.51

Discussion

The observed octanol water partition coefficient of indomethacin was found to be 3.56.

Compatibility Studies

General Appearance

Table 10: Compatibility studies (general appearance) of indomethacin.

Accelerated Environmental Conditions (40°C/75% RH)				
S. No.	**Sample**	**Zero Month**	**Three Month**	**Six Month**
1.	IN (Indomethacin)	Pale yellow crystalline powder	complies	Complies
2.	IN + GG (Guar gum)	Pale yellow crystalline powder	complies	Complies
3.	IN + EC (Ethyl Cellulose)	Pale yellow crystalline powder	complies	Complies

Discussion

On the bases of observations, it can be concluded that the indomethacin was compatible with the selected ingredients because there was no change in appearance on storage in accelerated environmental conditions.

IR Method

Table 11: Compatibility studies (IR method) of indomethacin.

Accelerated Environmental Conditions (40°C/75% RH)					
S. No.	**Sample**	**Observed peaks of Indomethacin (Zero Month)**		**Observed peaks of Indomethacin (Three Month)**	**Observed peaks of Indomethacin (Six Month)**
		Interpretation	**Peak**		
1.	IN (Indomethacin)	O-H C=O C=C C-H C-N C-O C-CO-O Aromatic ring	3371.34 1714.6,1691.46 1614.31,1479.30 1427.23 1371.29 1307.65 1234.36 1188.07,1147.57	Complies	Complies
2.	IN + GG (Guar gum)	O-H C=O C=C C-H C-N C-O C-CO-O Aromatic ring	3371.34 1714.6,1691.46 1614.31,1479.30 1427.23 1371.29 1307.65 1234.36 1188.07,1147.57	Complies	Complies
3.	IN + EC (Ethyl Cellulose)	O-H C=O C=C C-H C-N C-O C-CO-O Aromatic ring	3371.34 1714.6,1691.46 1614.31,1479.30 1427.23 1371.29 1307.65 1234.36 1188.07,1147.57	Complies	Complies

Discussion: On the bases of observations, it can be concluded that the indomethacin was compatible with the selected ingredients (guar gum and ethyl cellulose) because there was no addition or deletion of any peak as well as no shift of peak was observed in IR spectra on storage in accelerated environmental conditions. IR method is one of the most useful method for compatibility study testing.

Evaluation of prepared SR granules of Indomethacin

Flow Properties

Table 12: Flow properties of indomethacin SR granules (Trial batch).

S. No.	**IN-1**	**IN-2**	**IN-3**	**IN-4**	**IN-5**	**IN-6**	**IN-7**	**IN-8**
Bulk Density (gm/ml) (n=3)	0.884± 0.058	0.892± 0.080	0.889± 0.014	0.906± 0.036	0.898± 0.072	0.890± 0.031	0.883± 0.054	0.886± 0.047
Tapped Density (gm/ml) (n=3)	1.052± 0.024	1.067± 0.021	1.058± 0.049	1.084± 0.047	1.067± 0.018	1.085± 0.028	1.059± 0.030	1.063± 0.027
Angle of Repose (Degree) (n=3)	35.25± 0.40	35.25± 0.38	36.72± 0.34	36.20± 0.33	36.73± 0.47	35.54± 0.41	35.66± 0.34	35.28± 0.35
Compressibility Index (%) (n=3)	15.96± 1.27	16.40± 1.52	15.97± 1.24	16.42± 1.20	15.83± 1.31	17.97± 1.30	16.61± 1.41	16.65± 1.20

Discussion: On the basis of observation, it can be concluded that the prepared SR granules of indomethacin was having (angle of repose 35° to 36°, compressibility index 15% to 17%) good flow properties.

% Cumulative Drug Release of prepared SR granules of Indomethacin

Table 13: % Cumulative release of indomethacin SR granules (Trial batch).

Formulation	DR 5 min	DR 30 min	DR 1 Hr	DR 2Hr	DR 4Hr	DR 6Hr	DR 8Hr	DR 10Hr	DR 12Hr
IN1	0	10.20± 0.033	25.24± 0.048	50.14± 1.34	63.11± 0.050	75.41± 0.038	85.72± 0.047	98.26± 1.27	-
IN2	0	11.54± 0.074	26.48± 0.029	50.84± 0.037	65.78± 0.024	74.26± 0.033	86.38± 0.058	98.12± 0.084	-
IN3	0	10.00± 0.090	20.17± 0.070	46.22± 0.027	60.76± 0.020	71.83± 0.038	79.34± 1.28	83.65± 1.57	-
IN4	0	18.85± 0.038	35.80± 0.064	63.06± 0.058	71.15± 0.078	80.35± 1.75	97.25± 0.093	-	-
IN5	0	15.17± 0.032	28.76± 0.092	42.74± 0.058	69.00± 0.069	80.54± 1.47	95.23± 0.067	-	-
IN6	0	9.95± 0.049	20.35± 0.070	26.13± 0.058	40.72± 0.034	49.69± 0.063	68.10± 0.084	79.36± 0.058	96.81± 1.24
IN7	0	6.64± 0.043	26.27± 0.045	30.99± 0.058	49.91± 0.060	55.27± 0.072	69.78± 0.057	88.82± 0.076	95.79± 0.030
IN8	0	11.47± 0.12	15.77± 0.35	27.83± 0.71	50.85± 0.74	64.48± 0.92	70.22± 0.15	81.78±0. 97	97.89±0. 70

Discussion: For making sustain release indomethacin three polymers xanthan gum, guar gum and ethyl cellulose were selected. PVPK 30 was used as binder for wet granulation and lactose was used as diluent in the formulation. Magnesium stearate and talc were selected as lubricants. As per the table 7.26 formulation IN1-IN3 containing different ratios of polymers were released the drug upto 10 hrs. only. In case of IN4 & IN5 the concentration of PVPK 30 was reduced by which the drug is released in eight hrs. only. In IN6 and IN7 single polymer xanthan gum and ethyl cellulose was used respectively. Both the formulations showed drug release upto 12 hrs. At last formulation IN8 was prepared using guar gum with ethyl cellulose and it shows ideal and maximum release upto 12 hrs.

From above results it can be concluded that ethyl cellulose in combination with guar gum can be used to retard drug release. As the amount of PVPK 30 decreases the release of the drug increases.

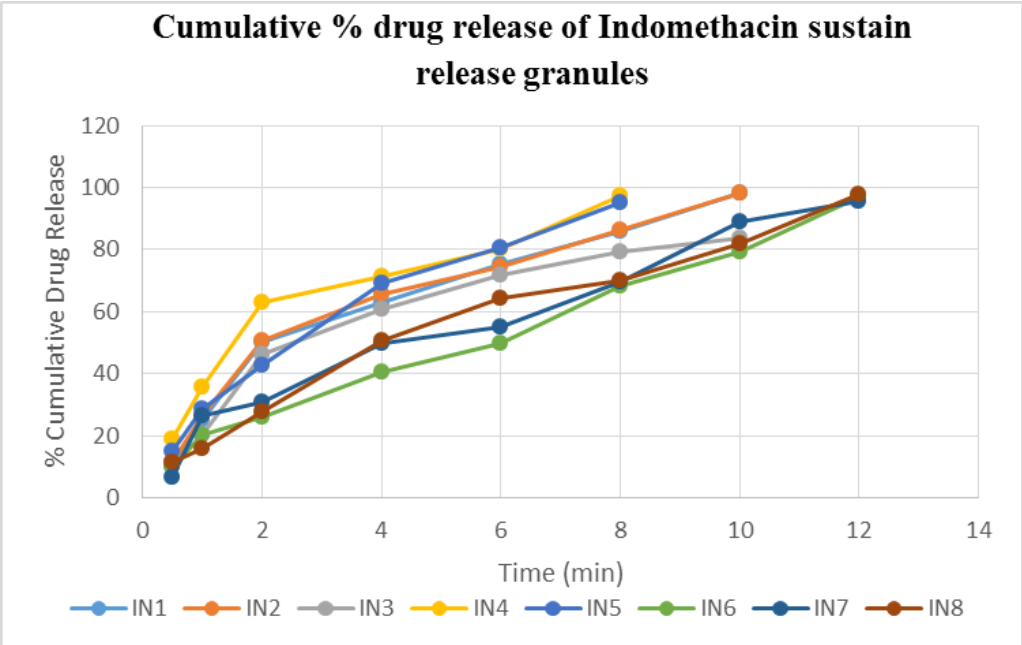


Fig 4: % Cumulative drug release of Indomethacin SR granules (Trial batch).

Evaluation of optimized SR granules of Indomethacin

Flow Properties

Table 14: Flow properties of indomethacin SR granules (Optimization batch).

S. No.	OIN-1	OIN-2	OIN-3	OIN-4	OIN-5	OIN-6	OIN-7	OIN-8
Bulk Density (gm/ml) (n=3)	0.886± 0.045	0.889± 0.182	0.881± 0.011	0.890± 0.148	0.887± 0.049	0.889± 0.038	0.880± 0.044	0.894± 0.025
Tapped Density (gm/ml) (n=3)	1.063± 0.012	1.069± 0.043	1.067± 0.034	1.069± 0.023	1.067± 0.088	1.063± 0.097	1.065± 0.041	1.070± 0.133
Angle of Repose (Degree) (n=3)	36.28± 0.073	36.21± 0.046	36.73± 0.074	36.54± 0.072	36.62± 0.045	35.80± 0.055	36.67± 0.251	36.32± 0.018
Compressibility Index (%) (n=3)	16.65± 0.081	16.83± 0.095	17.43± 0.028	16.74± 0.035	16.86± 0.158	16.36± 0.019	17.37± 0.012	16.44± 0.451

Discussion

The prepared SR granules of indomethacin was having (angle of repose 35° to 36°, compressibility index 16% to 17%) good flow properties.

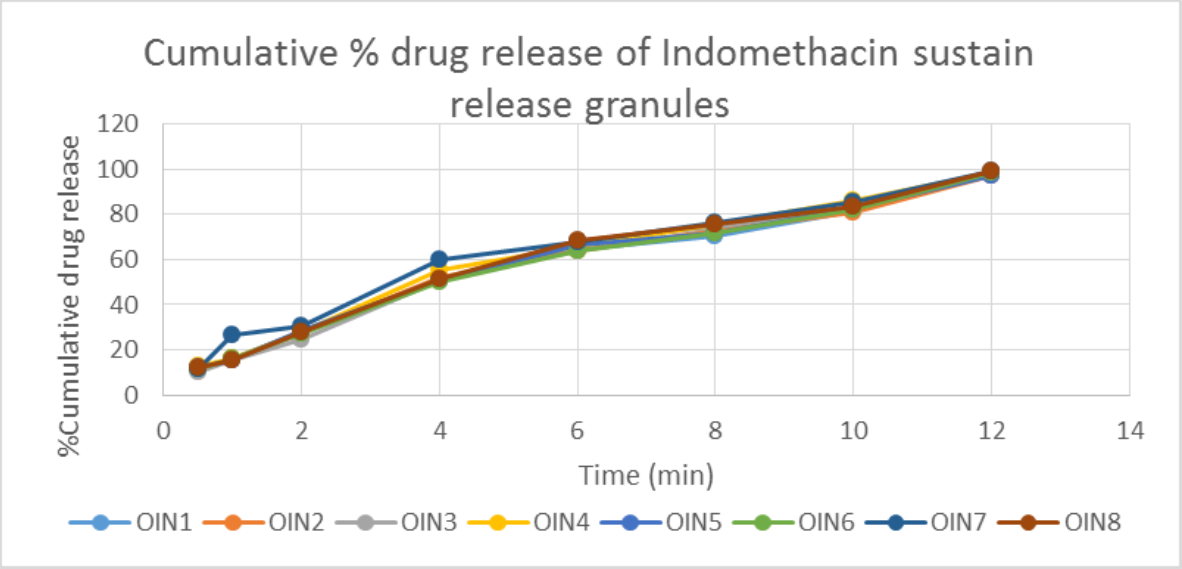


Fig 5: % Cumulative drug release of Indomethacin SR granules (Optimized batch).

Drug Release of optimized SR granules of Indomethacin.

Table 15: % Cumulative drug release of indomethacin SR granules (Optimization batch).

Formulation	DR 5 min	DR 30 min	DR 1 Hr	DR 2Hr	DR 4Hr	DR 6Hr	DR 8Hr	DR 10Hr	DR 12Hr
OIN1	0	11.47± 0.12	15.77 ±0.35	27.83± 0.71	50.85± 0.74	64.48± 0.92	70.22± 0.15	81.78±0. 97	97.89±0. 70
OIN2	0	11.29± 0.40	16.12 ±0.57	27.28± 0.78	52.14± 0.43	63.72± 0.19	72.93± 0.64	80.77±0. 58	97.26±0. 32
OIN3	0	10.34± 0.22	15.26 ±0.52	24.76± 0.80	50.57± 0.14	68.22± 0.37	74.15± 0.82	83.73±0. 81	98.53±0. 64
OIN4	0	12.85± 0.59	15.91 ±0.16	27.98± 0.74	55.13± 0.72	65.71± 0.68	75.74± 1.27	85.84±0. 46	98.72±0. 72
OIN5	0	12.25± 0.56	15.73 ±0.77	28.49± 0.74	50.87± 0.75	66.49± 0.54	71.99± 0.61	82.91±0. 58	97.05±0. 81
OIN6	0	11.48± 1.25	15.96 ±0.78	27.28± 0.59	50.41± 0.72	64.07± 0.74	71.82± 0.54	81.94±0. 23	98.84±0. 94
OIN7	0	11.76± 0.82	26.78 ±0.39	30.16± 0.42	59.95± 0.73	68.00± 0.61	76.36± 0.94	85.58±0. 22	99.26±0. 54
OIN8	0	11.83± 1.85	15.71 ±0.46	28.00± 0.50	51.32± 0.26	68.55± 0.75	75.44± 0.30	83.47±0. 93	99.15±0. 79

Discussion: From all the initially prepared eight (IN1-IN8) trial batch formulations IN8 was selected for further optimization. Again eight formulations were prepared by using different concentrations of ethyl cellulose, PVPK30 and guar gum. In formulation OIN1 to OIN8 it was observed that as the concentration of PVPK30 was decreased the release of the drug was increased whereas as the concentration of ethyl cellulose and guar gum was increased the release of the drug was decreased. Formulation OIN7 and OIN8 were showed the satisfactory release, but in OIN 8 the release rate was ideal and maximum. It was due to the increased concentration of guar gum (Twice as compared to OIN7). So OIN8 was selected as the best formulation and used for the further study.

***Ex vivo* permeation study**

From the above graph of *ex vivo* study it can be concluded that the optimized formulation (IN8) showed better release profile then marketed formulation. The marketed formulation selected was sustained release tablet. It was first crushed to form suspension with Krebs ringer solution.

Table 16: Concentration after ex vivo permeation study of marketed and optimized indomethacin formulation.

Time (hrs)	OIN 8	Marketed
0.5	20.24	18.25
1	25.87	26.69
2	44.84	35.48
4	62.11	52.78
6	70.58	65.71
8	80.42	73.28
10	87.06	79.11
12	99.15	97.52

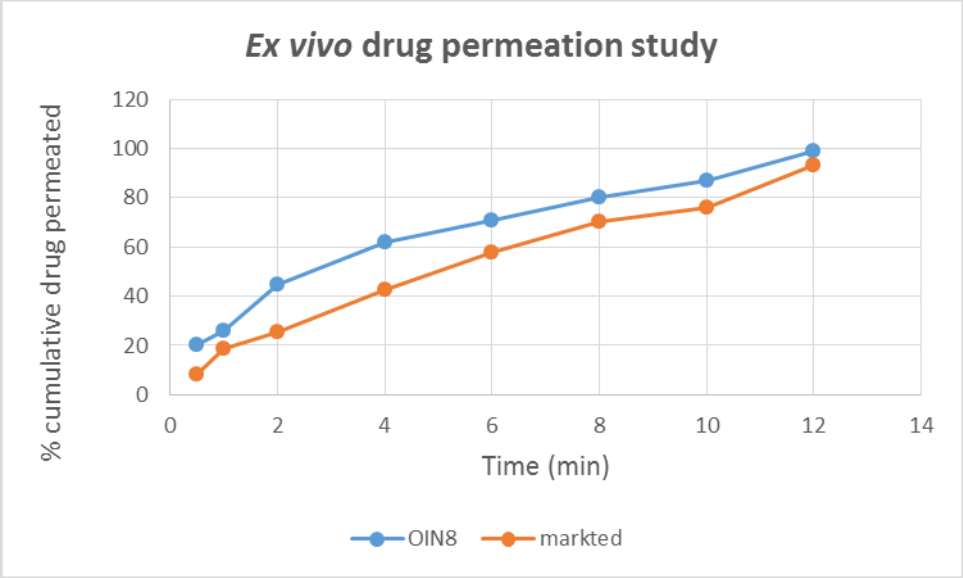


Fig 6: Ex vivo permeation study of marketed and optimized indomethacin formulation.

Statistical Analysis of SR Indomethacin Optimized Formulation

ANOVA

Table no 17: Analysis of variance (ANOVA) of Sustain Release Indomethacin for dependent variables from factorial design using SPC.

Factors	Sum Square	Degree of Freedom	Mean Square	F Value	p Value
Ethyl Cellulose	0.253	1	0.253	0.907	0.0037
Guar Gum	0.012	1	0.012	0.008	0.0214
PVPK-30	3.735	1	3.735	13.413	0.0061
Polynomial	$y = 0.0179x^4 - 0.3911x^3 + 2.0977x^2 + 7.7858x + 6.9117$				

Discussion: On the bases of statistical results it can be concluded that there was significant difference between concentration of Ethyl cellulose, guar gum and PVPK-30 on drug release, as the p value was less than 0.05.

Response surface model

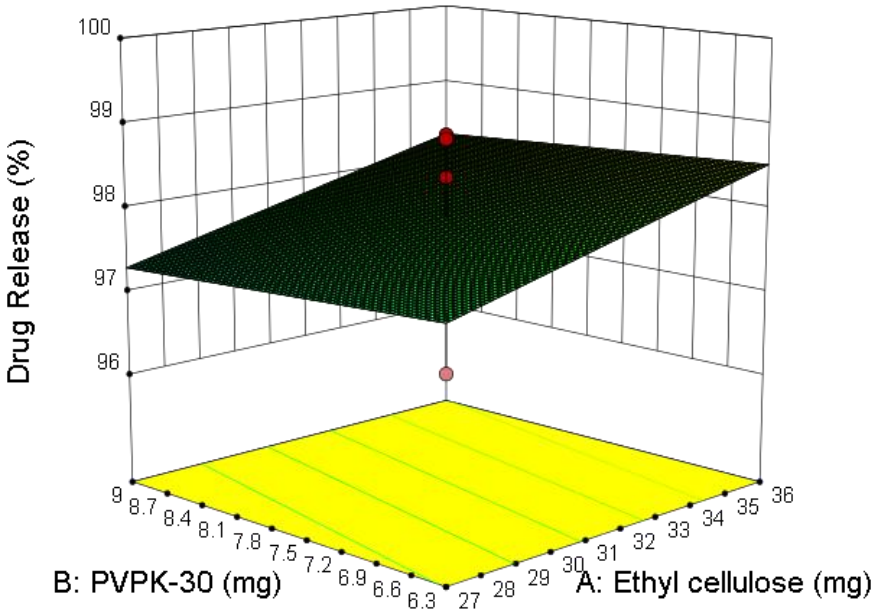


Fig 7: Response surface model showing the effect of PVPK 30 and ethyl cellulose on drug release of Indomethacin.

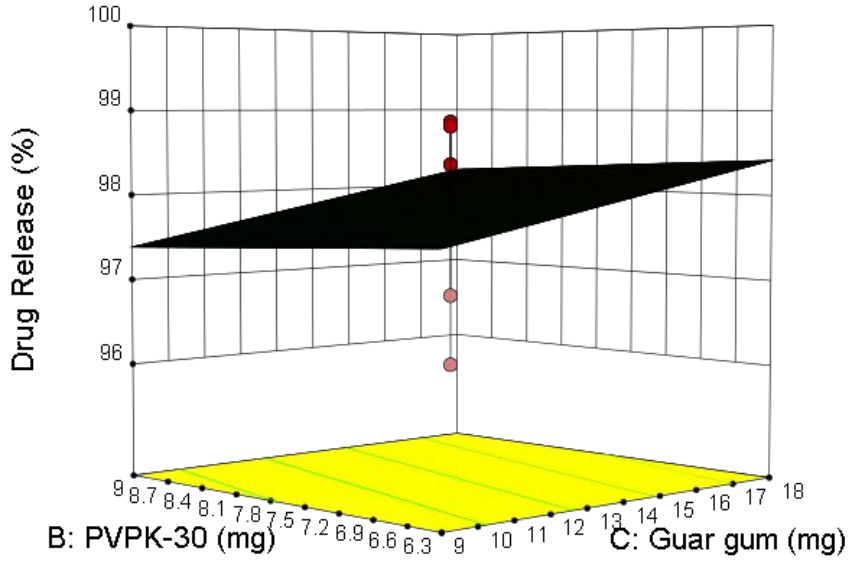
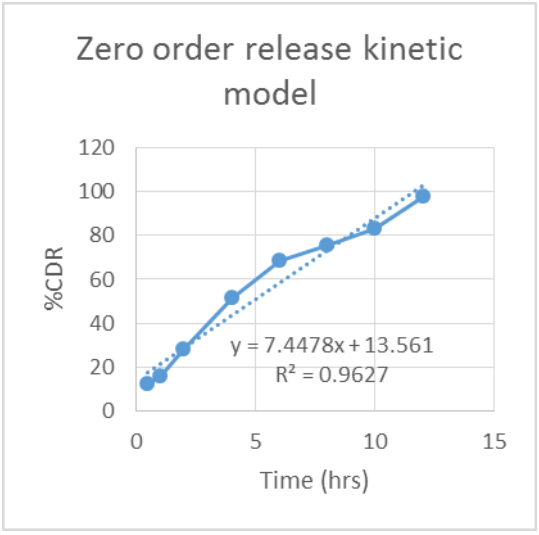


Fig 8: Response surface model showing the effect of PVPK 30 and guar gum on drug release of Indomethacin.

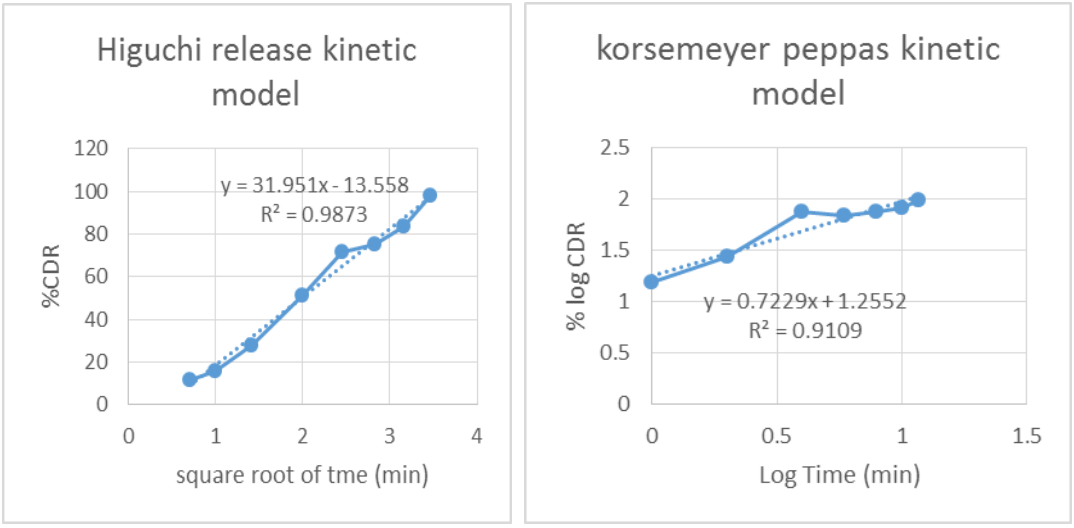
Discussion: As per the fig 7.21 and 7.22 the high level of PVPK 30 shows low value of % age drug release which indicates significantly negative effect on drug release. Whereas Guar gum and ethyl cellulose shows high value of % drug release at their high level, which indicates significant effect on drug release.

Mathematical Model



(A) **(B)**

Fig 9: Zero order (A) & First order (B) kinetic model of SR Indomethacin (OIN8)



(A) **(B)**

Fig 10: Higuchi (A) & Korsemeyer peppas (B) release kinetic model of Sustain Release Indomethacin (OIN8)

Table no 18: Mathematical model of drug release profile on Sustain Release Indomethacin.

Formulation	Regression values				
	Zero order	First order	Higuchi	Korsmeyer peppas	Release exponent (n)
OIN1	0.9610	0.9929	0.9824	0.9099	0.793
OIN2	0.9568	0.9728	0.9732	0.9038	0.771
OIN3	0.9611	0.9703	0.9856	0.8952	0.827
OIN4	0.9556	0.9845	0.9836	0.9036	0.785
OIN5	0.9658	0.9937	0.9728	0.9093	0.774
OIN6	0.9628	0.9846	0.9813	0.9432	0.782
OIN7	0.9254	0.9907	0.9854	0.8940	0.781
OIN8	0.9627	0.9929	0.9873	0.9109	0.722

Discussion: As per the results in table no 7.36 it can be concluded that the drug release profile of sustain release indomethacin formulation followed first order release model, as the R^2 was found to be highest (0.9703 to 0.9929). The value of release exponent (n) was 0.771 to 0.827 which indicates non fickian diffusion mechanism of the optimized formulation.

EVALUATION OF OPTIMIZED CAPSULE FORMULATION (CP1)

Table 19: Evaluation of optimized In-situ capsule formulation.

General appearance	Weight variation (mg)	Avg. Wt. (mg)	D.T. (min)	DR 30 min (IN)	DR 2 Hr (IN)	DR 6 Hr (IN)	DR 10 Hr (IN)	DR 12 Hr (IN)
Yellow Cap and Body	Max+ 4.15 Min -0.15	301.42	12±2	10.52	28.00	67.55	82.17	99.84

Discussion: by using optimized formulations (optimized buffer, OP8 and OIN8) capsules were then prepared. The prepared capsule showed almost same release rate as the optimized granules. So CP1 was the final formulation which was then compared with the marketed formulation.

COMPARISON OF OPTIMIZED FORMULATION WITH EXISTING MARKETED FORMULATION:

A comparison was made between marketed formulation and the optimized formulation ION-8 based on drug release pattern (Table 14). As per the search, there was no such formulation available on the market so indomethacin SR granules were compared with marketed SR indomethacin capsule **(Indocap SR capsule: Jagsonpal Pharmaceuticals Ltd.)**.

On the basis of observation, it can be concluded that in prepared optimized formulation indomethacin SR has better release rate with the immediate release pantoprazole, as compared to the selected marketed formulation.

Table 20: Comparison of Optimized Formulation with Existing Marketed Formulation.

Formulation	DR 15 min (PN)	DR 30 min (PN)	DR 30 min (IN)	DR 1 Hr (IN)	DR 2 Hr (IN)	DR 4 Hr (IN)	DR 6Hr (IN)	DR 8Hr (IN)	DR 10 Hr (IN)	DR 12 Hr (IN)
Marketed	0	0	13.44	18.25	22.23	39.16	58.88	67.63	77.24	96.08
CP1	82.04	98.8	10.52	15.12	28.00	51.32	67.55	73.44	82.17	99.84

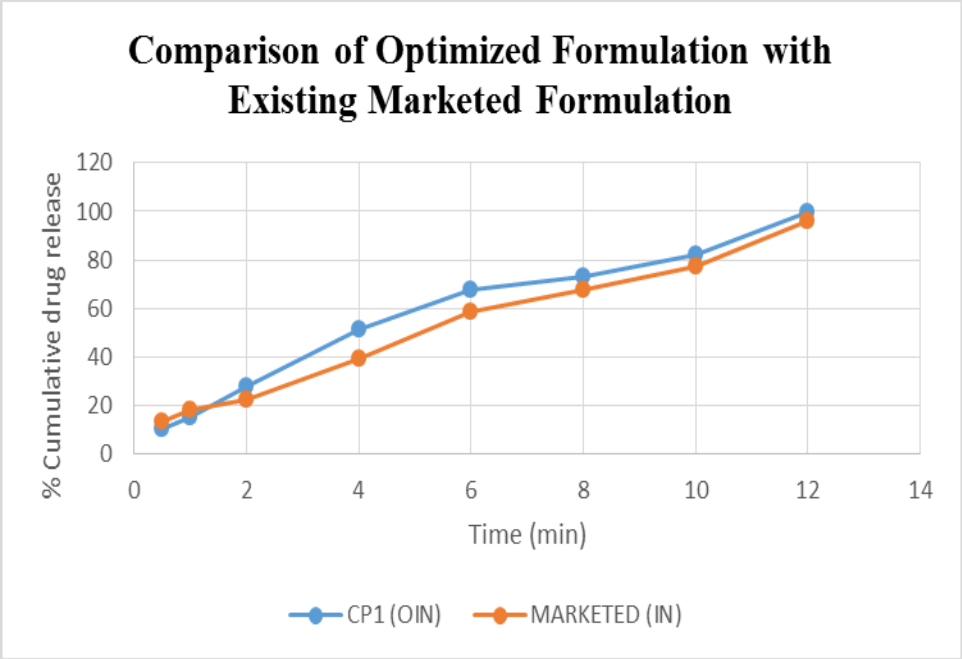


Fig 11: Comparison of Optimized Formulation with Existing Marketed Formulation.

ACCELERATED STABILITY STUDIES (ICH: 40 ± 2°C TEMP. & 75 ± 5% RH) OF OPTIMIZED FORMULATION (OIN-8)

Optimized formulation (Formulation ION-8) was subjected to accelerated stability testing as per the ICH guidelines. For this, the prepared capsules were placed in a humidity chamber at 40 ± 2°C temp and 75 ± 5% RH for 6 months. The samples were tested for stability at 0, 3 and 6 months on the bases of general appearance and *in vitro* drug release.

Table 21: Accelerated Stability Studies of Optimized Formulation (OIN-8).

Time	General appearance	DR 30 min (IN)	DR 1 Hr (IN)	DR 2 Hr (IN)	DR 4 Hr (IN)	DR 6Hr (IN)	DR 8Hr (IN)	DR 10 Hr (IN)	DR 12 Hr (IN)
Zero Month	Yellow Cap and Body	10.52	15.12	28.00	51.32	67.55	73.44	82.17	99.84
Three Month	Yellow Cap and Body	9.75	14.86	27.44	49.71	66.42	74.72	82.33	99.43
Six Month	Yellow Cap and Body	11.02	15.34	28.92	49.47	67.83	73.26	82.97	99.05

DISCUSSION

On the basis of observation, it can be concluded that the optimized formulation (OIN-8) was the stable because there was no change was observed in general appearance as well as in drug release when exposed to accelerated environmental conditions.

CONCLUSION

On the bases of above research, it can be concluded that the designed capsule formulation containing indomethacin (NSAIDs) can be used as anti-inflammatory for the inflammatory diseases such as gout arthritis etc. the designed formulation is stable and it has novel combination of ingredients. Further work can be done to reduce the size of the capsule.

REFERENCE

1. Nonsteroidal anti-inflammatory drug [Internet]. En.wikipedia.org. 2015 [cited 10 dec 2015].Availablefrom:https://en.wikipedia.org/wiki/ Nonsteroidal_antiinflammatory_drug
2. Dhikav V, Singh S, Pande S. Non-Steroidal Drug-induced Gastrointestinal Toxicity: Mechanisms and Management. Indian Academy of Clinical Medicine, 2003; 4(4): 315-322.
3. G.Sahitya, B.Krishnamoorthy, M.Muthukumaran, Importance of Preformulation Studies In Designing Formulations For Sustained Release Dosage Forms, International Journal of Pharmacy &Technology, 2013; 4(4): 2311-2331.
4. Sonali S Bharate, Ram A Vishwakarma, Impact of preformulation on drug development, Expert Opinion on Drug Delivery, 2013; 10(9): 563-578.
5. ICH Harmonised Tripartite Guideline, Stability Testing of New Drug Substances and Products Q1A(R2): 2003.
6. http://www.particlesciences.com/docs/DDT-Particle_Size_Dist-May_09.pdf accessed on 5 jan 2016.
7. Kwon Y (2001). "4.2.4: Partition and Distribution Coefficients". Handbook of Essential Pharmacokinetics, Pharmacodynamics and Drug Metabolism for Industrial Scientists. (secondary). New York: Kluwer Academic/Plenum Publishers, 44
8. Rubi Singh, Pramod Kumar Sharma, Prashant Dhakad, Preformulation Studies of Pantoprazole Sodium Susquihydrate for Sustained Release Mucoadhesive Microsphere, Global Journal of Pharmacology, 2014; 8(4): 547-550.
9. Gita Chaurasia, A Review On Pharmaceutical Preformulation Studies In Formulation And Development Of New Drug Molecules, International Journal of Pharmaceutical Sciences and Research, 2016; 7(6): 2313-2320.
10. Sonali S. Bharate, Sandip B. Bharate, Amrita N. Bajaj, Interactions and incompatibilities of pharmaceutical excipients with active pharmaceutical ingredients: a comprehensive review.Journal of Excipients and Food Chemistry, 2010; 1(3): 3-26.
11. Joseph B. Schwartz *et al*., Optimization techniques in product formulation, Journal of the society of cosmetic chemists, 1981; 32: 287-30.
12. Ahmed Allam N, Komeil A, Abdallah O. Tailor Made Phospholipid Based Curcumin Phytosomes: Fabrication, Characterization and Ex-Vivo Permeation. IOSR Journal of Pharmacy and Biological Sciences, 2016; 11(3): 120-127.
13. Narmada GY, Mohini K, Prakash Rao, Gowrinath, kumar K, Formulation, Evaluation and Optimization of Fast Dissolving Tablets Containing Amlodipine Besylate by Sublimation Method,Ars Pharm, 2009; 50(3): 129-144.
14. Manish Jaimini, Sonam Ranga, Amit Kumar, Sanjay Kumar Sharma, Bhupendra Singh Chauhan, A Review on Immediate Release Drug Delivery System by Using Design of Experiment, Journal of Drug Discovery and Therapeutics, 2013; 1(12): 21-27.
15. Ramteke H, Dighe A, Kharat A, Patil S, Mathematical Models of Drug Dissolution: A Review, Sch. Acad. J. Pharm, 2014; 3(5): 388-396.