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DESIGN, DEVELOPMENT, OPTIMIZATION AND EVALUATION OF NATURAL GUM BASED MATRIX TABLET OF INDOMETHACIN

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ABSTRACT

The main objective was to develop matrix tablets (Sustained release) of IM (indomethacin by the help direct compression method. IM (Indomethacin is a NSAID'S (non-steroidal Anti-inflammatory drug's). Indomethacin (IM) is a COX (cyclooxygenase) inhibitor. IM (sustained) release matrix of IM (Indomethacin) was formulated by the help of relatively less used matrix forming material Gum copal and gum damar. IM(Indomethacin) solid dispersion was prepared by the of PEG4000 and PVPK30.The dissolution(rate) of IM(Indomethacin) is first enhanced by the help of dispersion the drug in hydrophilic polymer(PEG)4000 and the dispersion is the enclosed in the matrix of gum copal and gum damar. Indomethacin separate ration of Indomethacin (IM) and gum copal were engaged and the dispersion (solid) were prepared by melting and solvent method. IR (Infrared spectroscopy) studies display that there are no any interaction among IM (Indomethacin) and PEG4000.The granules appears good flow characteristics and test carry out within the standards.

KEYWORDS: INDOMETHACIN, GUM DAMAR, GUM COPAL, PEG-4000, MATRIX TABLET, SUSTAINED RELEASE, PVPK30.

INDTRODUCTION

Sustained release dosage form is most broadly formulated for maintain blood (therapeutic) and level (tissue) of the drug (API) for extended duration of time accompanied by reducing systemic or local adverse effect. Designing of sustained release dosage form gives a consistent (constant) concentration or quantity of drug (API) at site of absorption) and also maintains the concentration (plasma) through the therapeutic range, reduces the side effects and decrease the frequency of administration of drug.[1] Formulation of sustained release by the help of matrix method is most widely used method because of the relieve of formulation pliability and low cost effective. Hydrophilic (water soluble) matrices are most widely used as oral delivery of drug system despite of their better compatibility.[2] Release of drug form hydrophilic matrix (tablets) is managed by emergence of a viscous (hydrated) bed on all sides of Tablets, which behaves as a boundary to release of drug by contending penetration of water into tablet and also flow of solutes (dissolved) gone away of the matrix tablets. The release of drug process is affect by solubility of drug and mechanical and physical characteristics of the boundary (gel) that forms all sides of tablets.[8] Natural gums are adopted beyond synthetic substances because of their, non-noxious, cost effective and better availability. IM (Indomethacin is a prescription medication and used as non-steroidal anti-inflammatory drugs (NSAID'S). Mechanism of IM (Indomethacin) is that it inhibits the formation of prostaglandin, signalling molecules (Indigenous).Indomethacin (IM) is used for the treatment of Osteoarthritis and Arthritic gout.[4] Chemical name of IM (Indomethacin) is 1-(4-Chlorobenxoyl)-5-methoxy-2-methyl-1 H- indole-3- acetic acid.[4,7] Indomethacin (IM) sustained release matrix tablet reveal enhance therapeutic action i.e. release of drug over extended duration of time by delivering a dose (single).[3] The development of matrix tablet attained a lot of benefits beyond conventional dosage form such as improvement in patient compliance[4] and in systemic circulation amount of drug is reduced. Indomethacin (IM) solubility in alcohol and insoluble in aqueous medium.[7] Gum copal and gum Damar is used in the formulation of IM (Indomethacin) matrix tablet which behaves as matrix forming materials. Selection of gum copal due to its non-noxious nature and easily compressed and better swelling characteristics.[5,6] PEG4000 and PVPK30 is used as carrier in the formulation of Indomethacin (IM) solid dispersion system.

MATERIALS AND METHOD

The Indomethacin was purchased from Dhamtec Pharma and consultants, Mumbai. Polyethylene glycol-4000 (PEG 4000) and Polyvinyl Pyridine K30 (PVP K30) Gum copal

and Gum damar purchased from Vigyan Kendra, Varanasi. All other reagents and Chemicals were used of analytical reagent grade.

PREPARATION OF SOLID DISPERSION

Melting fusion were used for the preparation of solid dispersion of Indomethacin using PEG-4000 and PVPK30. The proportions of various types of ingredients used in the preparations are given in table 1.

Table 1: Formulation chart for Solid dispersion of Indomethacin.

S. No.	Drug Polymer Ratio	Indomethacin(mg)	PEG 4000(mg)	PVPK 30(mg)
1.	3:2	75	50	
2.	3:4	75	100	
3.	3:6	75	150	
4.	3:2	75		50
5.	3:4	75		100
6.	3:6	75		150

PROCEDURE

The drug and polymer was heat till the polymer melts. After that the molten mixture were stirred properly till the drug were Stirred properly till the drug were dissolved totally in the melt and then we obtained a homogenous solution. The solution(homogenous) were kept to solidity by pouring it to would of tablets under suitable ambient conditions, for fast solidify at very less temperatures different types of preparations were formulated by using different concentration of polymer. The concentration of drug (API) were kept constant that is 75mg while the polymer concentration were vary from 50mg, 100mg, 150mg etc. And giving the preparations with drug: polymer rations 3:2, 3:4, 3:6 respectively by using PEG4000 and PVPK30 the solid dispersion formulated further. These were subjected for evaluation.

MICROMETRIC EVALUATION OF SOLID DISPERSION

Bulk Density and Tapped Density

Solid dispersion required amount was weighed and transfer in a measuring cylinder and the volume was noted. Then it was tapped for 100 times from a uniformity elevation (height) and then tapped volumes were estimated.

$$\mathbf{D} = M/V$$

Where, M = Mass

V = volume

Bulk density = Bulk mass / Bulk volume

Tapped density = Bulk mass / Tapped volume

Carr's index (compressibility)

Flow ability of the preparation can be calculated by using the formula which is given below:

Carr's index= Tapped density – bulk density/ Tapped density ×100

Hausner's ratio

It is determined by following formula:

Hausner's ratio = tapped density / bulk density

Angle of repose

It is the most common method of determining flow property of powder and granules. The angle of repose of solid dispersion calculated by funnel method. The solid dispersion of IM (Indomethacin) was permit to flow out of the orifice of funnel on a plane (paper) which is placed on the horizontal surface. This builds a pile on paper.

$$\mathbf{Tan\theta}=h/r$$

Evaluation of Solid Dispersion

Determination of drug content of solid dispersion

The different types of batches were formulated by using PEG4000 and PVPK30 was taken for analysis of drug content in solid dispersion. Weigh accurately 75mg drug containing solid dispersion was powdered properly and these were passed through the sieve number 85/120. The remaining retained powder on the 120 sieve no. Were mixing in appropriate amount of phosphate buffer solutions (PH 7.4).Then solution were filtered by the help of filter paper. Now from this 100 ml solution were pipette out and transfer in standard volumetric flask of 100 ml and by help of phosphate buffer (PH 7.4) made up to required volume. These were estimated by using uv-visible spectrophotometer for drug content at 320 nm. Drug content were calculated for four samples from the same batch for each of the ratio and for each of the method.

Solubility studies of solid dispersion

A prepared solid dispersion of drug and different polymer (PEG4000 and PVPK30) were prepared in different ratio. Then it was transfer in a screw capped bottles which contains distilled water. Then these bottles (screw capped) was shaken mechanically at 26^0C for 24 hrs

(time duration). After than an aliquots' amount are taken out, filtered and analyzed of drug content at 320nm.

In vitro dissolution study of Solid Dispersion

Dissolution were obtained by using type -2 apparatus (USP) (DBK instruments Mumbai) in the Phosphate buffer of PH 7.4 (900 ml) as medium, at temperature of 37±0.5ºC and at 75 round per minute. All preparations equal to 75mg of Indomethacin were put in dissolution media and sample (5 ml) were taken out at time of 5 min, 10 min, 15 min, 20 min and 30 min and it was diluted up to 50 ml and then these were analyzed with uv-spectrophotometer. Cumulative releases of drug were calculated and it was compared with dissolution of pure drug.

Formulation of 75mg indomethacin matrix tablets

Table 2: Composition of Indomethacin Matrix Tablet.

Ingredient in (mg)	F1	F2	F3	F4	F5	F6
Solid Dispersion Equivalent to 75mg	225mg	225mg	225mg	225mg	225mg	225mg
Gum Copal	35	25	20			
Gum Damar				30	40	45
Microcrystalline cellulose	29	39	44	34	24	19
Talc	5	5	5	5	5	5
Magnesium Stearate	6	6	6	6	6	6
	300mg	300mg	300mg	300mg	300mg	300mg

Procedure for preparation of indomethacin matrix tablet

The formula for various matrix tablets were prepared as shown in table 4.The solid dispersion and gum copal are first mixed in mortar and pestle and retaining of the ingredients were added, mixed properly and the resultant mixture were subjected to direct compression tablet punching machine. On the other hand, matrix tablets prepared by using gum damar the solid dispersion is first blended properly in gum damar and then it was blended with remaining ingredients and these are taken to direct compression.

Evaluation of indomethacin matrix tablet

Pre compression study

Evaluation of granules

Bulk density and Tapped density determination

Granules were weighed accurately and it was transfer in a measuring cylinder and the volumes (VB) were measured. After that the measuring cylinder we locked by the help of a

lid then it was placed in density determination equipments. The density equipment were set for 100 taps, after that the volume (V_t) were measured. The bulk density and tapped density were calculated by using following formula:

Bulk density = Weight of Granules/ V_B

Tapped density = Weight of Granules/ V_t

Where, $\mathbf{V_B}$ = Initial volume

$\mathbf{V_t}$ = Final volume

Carr's compressibility index

Carr's compressibility index is very important for determining flow ability of powder. Carr's compressibility index calculated from bulk density and tapped density. It can be calculated by using formula:

Carr's index =TD-BD/TD×100

Where, TD = Tapped density

BD = Bulk density

Hausner ratio: It shows that flow ability of granules. It is calculated by dividing tapped density and bulk density

Hausner ratio = Tapped density/Bulk density

Angle of repose

Angle represents the flow ability of Granules. Angle of repose was calculated by using funnel method. The funnel was inclined vertically in a funnel stand and below a Graph paper was placed. A granule was poured in the funnel and it was fall on Graph paper. The angles of repose were calculated by the help of Radius of pile and the base of the pile. Angle of repose is calculated by using formula.

Tan θ = h/r

Where, θ = Angle of repose

h = height of pile

r= radius of base of the pile

Post compression study

Hardness

Hardness is the crushing strength test. Hardness of tablet calculated in kg/cm^2.For controlled and sustained release of tablet it has hardness more than 8-12 kg/cm^2A tablets are put

between the two anvils. In two anvils force was applied and crushing strength which causes tablet to break was recorded.

Thickness

Thickness of the 10 tablet was measured by the help of Screw-Gauze.

Weight variation test

20 tablets was collected at randomly from a tablet batch and determining their individually weights. Average Weight was calculated. The individual weights are compared with average weight. By Formula, % weight variation calculated.

% weight variation = (IW-AW) X 100/AW

Where, IW = Initial weight

AW = Average weight

% Friability

Roche Friabilator is the apparatus used for the testing of friability of the tablet.20 tablets are weight altogether(w1).Then these tablets were put in Friabilator and instrument was adjusted at 100 rpm (round per minute) i.e. 25 rpm for 4 min. During each and every revolution the tablets falls from a distance of 6 inch. After 4 min tablets were removed from the chamber and weighed (w2) .The difference in W1 and W2 given weight loss (i.e. friability).

% Friability = Initial WT (W1) – Final WT (W2)) x100/Initial WT

OR

% **Weight loss** = (W1-W2) x100/W1

Where, **W1** = Initial Weight,

W2 = Final Weight

For compressed tablet,

Limit, % Friability = Not more than 1%

Drug content

75mg of indomethacin(IM) which containing formulations(300mg)was dissolved properly 7.4pH phosphate buffer for producing 100ml of solutions .The subsequent solution(10ml) was diluted to 100 ml along phosphate buffer(PH 7.4). After that it was analysed for Indomethacin (IM) content by calculating the absorbance (318nm).

In-vitro Dissolution studies of formulated tablet

Drug release study from the formulated matrix tablets were done by the help of USP dissolution test paddle type-2 apparatus (DBK Instruments Mumbai) in phosphate buffer (PH 7.4), 900 ml (medium) at 75 round per minute (rpm) and temperature was 37±0.5 C .75mg of IM(Indomethacin) was put in dissolution media and sample(5ml) was withdraw at different time min interval of 5,10,15,20,25,30 respectively and it was replaced y fresh medium, and the samples were filtered and absorbance was calculated at 318nm.

Accelerated stability of Indomethacine Tablets

The optimized preparations of indomethacin (IM) tablet were subjected for stability studies. The stability study was done at 40^0C +/- 2^0C/75%+/-2% RH for a period of 45 days. Tablets were alone packed in a aluminium foil and it was then packed in a amber coloured bottle and these we put in a chamber (heating humidity) for 45 days. The tablet was analyzed for hardness, appearance thickness, % Drug content and in vitro drug release.

RESULTS AND DISCUSSION

Micromeritic evaluation of solid dispersion

The Micromeritic evaluation of solid dispersion was characterised with respect (w.r.t) to bulk density, tapped density, Hausner's ratio, Carr's compressibility index and angle of repose.

Table 3: Micromeritic evaluation of solid dispersion.

Formulation (±SD)						
	PEG4000			PVPK30		
Batches/ Parameters	**B1**	**B2**	**B3**	**B4**	**B5**	**B6**
Bulk density (g/cm^3)	0.54±0.02	0.52±0.02	0.56±0.01	0.51±0.01	0.50±0.03	0.53±0.04
Tapped density (g/cm^3)	0.67±0.03	0.60±0.02	0.61±0.03	0.58±0.02	0.59±0.04	0.6. ±0.02
%Carr's Index	19.40±0.02	13.33±0.04	8.19±0.03	12.06±0.04	15.25±0.03	11.66±0.02
Hausner Ratio	1.24±0.02	1.15±0.03	1.08±0.01	1.13±0.01	1.18±0.02	1.13±0.02
Angle of Repose(θ)	29±0.01	28±0.02	27±0.01	29±0.01	30±0.02	31±0.01

The values obtained, these were lies within the range of acceptable and there is no difference found between bulk density and tapped density. The results may beyond affect the compressibility and dissolution of tablet. The % of compressibility of mixture of powder were calculated by Carr's compressibility index as shown in Table 3. All the preparations have excellent and good compressibility Hausner ratio were found between the range of 1.08

to 1.24 within shows the good flow and excellent flow properly. The angle of repose result was found to be in 27 to 31 indicates the excellent and good flow properties and was further supported compressibility (lower) into the values. The formulation drug: polymer ratio (3:6) with IM: PEG4000 have excellent flow property, good compressibility index.

Solubility Studies of indomethacin solid dispersion

Table 4: Solubility study of indomethacin solid dispersion of PEG4000.

PEG4000		
S. No.	**Drug polymer ratio**	**Solubility in water(mg/ml)(±SD)**
1.	**3:2**	0.189±0.011
2.	**3:4**	0.325±0.014
3.	**3:6**	0.592±0.018

Table 5: Solubility study of indomethacin solid dispersion of PVPK30

PVPK30		
S.no.	**Drug polymer ratio**	**Solubility in water(mg/ml)(±SD)**
1.	**3:2**	0.161±0.014
2.	**3:4**	0.311±0.011
3.	**3:6**	0.569±0.017

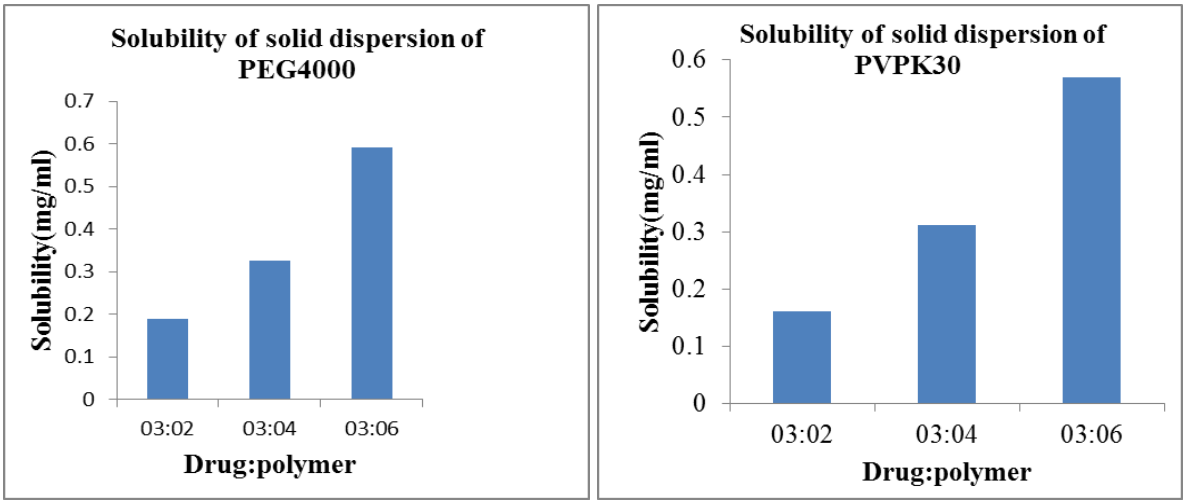

Fig. 1: Solubility study of solid dispersion of PEG4000 and PVPK30.

The solubility of Drug: PEG4000 (1:5) was found to be very good Compare to other Drug polymer ratio .So Drug: PEG 4000(1:5) was used in the formulation of 75mg matrix tablet of indomethacin because of good solubility as shown in Figure 1.

Determination of drug content

Drug content were calculated by the help of equation taken from the calibration curve of Indomethacin (IM) in phosphate buffer(PH7.4).Drug content in solid dispersion formulated

by using PEG4000 and PVPK30 and calculated by using equation **(y= 0.021X+ 0.001).** Preparation containing PEG4000(3:6) shows highest % of drug content that is 99.77% as compared to other formulations.

Table 6: % Drug content for PEG4000.

Batches	Formulation ratio	% drug content PEG4000
B_1	3:2	93±0.42
B_2	3:4	95±0.16
B_3	3:6	99±0.18

Table 7: % Drug content for PVPK30.

Batches	Formulation ratio	% drug content PVPK30
B_4	3:2	91±0.74
B_5	3:4	93±0.64
B_6	3:6	95±0.84

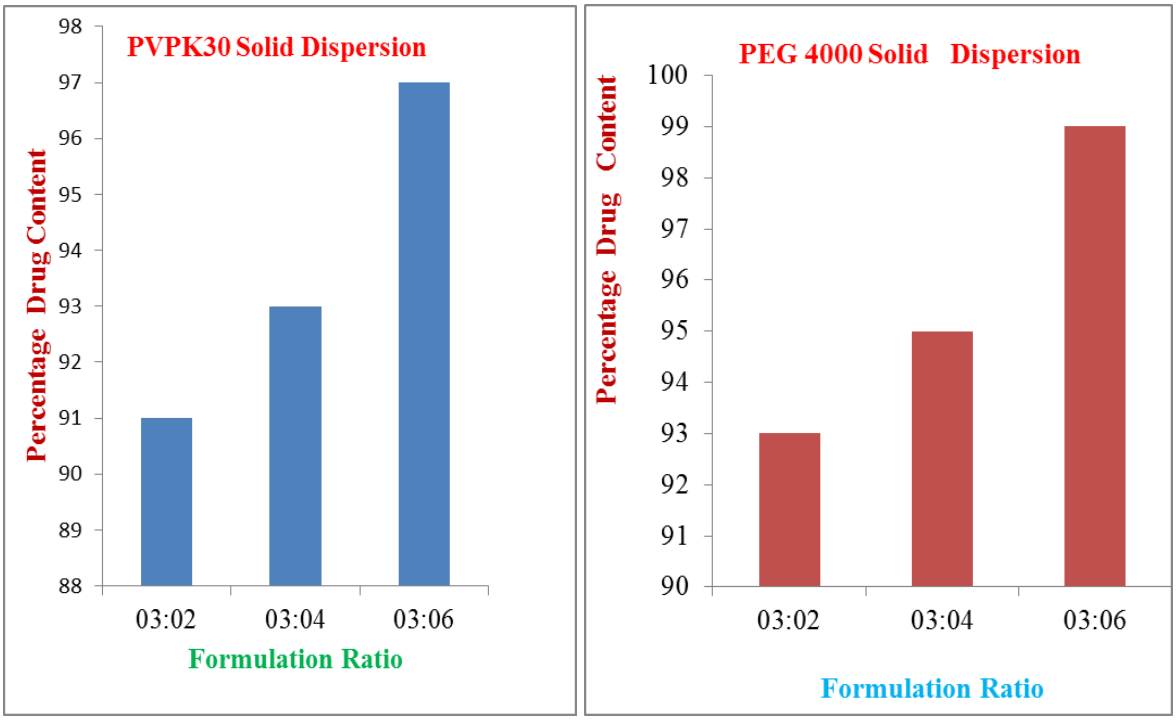

Fig. 2: Percentage Drug Content for PVPK30& PEG4000.

The solid dispersion batch (B_3) Drug: Polymer (3:6) showed maximum drug content (99.77) and drug release [98%] within 60 minutes, among all the preparations and this ratio can be used for enhancing the solubility and dissolution rate of poorly water soluble drug indomethacin it was seen that drug release were increased with increasing the quantity of polymer ratio.

Table 8: In-vitro drug release of study of solid dispersion containing drug and carries for various for formulations.

Cumulative % of drug released(±SD)						
	PEG4000			PVPK30		
Time(min.)	B1	B2	B3	B4	B5	B6
0	0	0	0	0	0	0
5	10±0.28	11±0.27	12±0.13	10±0.16	11±0.15	10±0.12
10	22±0.33	20±0.35	19±0.32	21±0.20	19±0.17	20±0.27
15	44±0.32	34±0.24	23±0.63	42±0.30	33±0.50	28±0.45
20	49±0.23	46±0.32	30±0.25	47±0.20	45±0.60	35±0.36
25	54±0.68	53±0.62	36±0.15	52±0.62	54±0.58	46±0.24
30	60±0.63	64±0.55	48±0.35	58±0.70	60±0.90	51±0.38
35	64±0.93	76±0.48	53±0.26	63±0.33	64±0.22	63±0.32
40	69±0.53	80±0.26	68±0.28	69±0.36	68±0.28	67±0.44
45	72±0.36	83±0.31	79±0.26	71±0.75	73±0.35	72±0.36
50	78±0.43	88±0.24	81±0.48	77±0.28	78±0.39	77±0.28
55	82±0.65	90±0.38	92±0.16	80±0.47	85±0.45	81±0.56
60	86±0.40	92±0.42	98±0.32	83±0.85	90±0.48	85±0.38

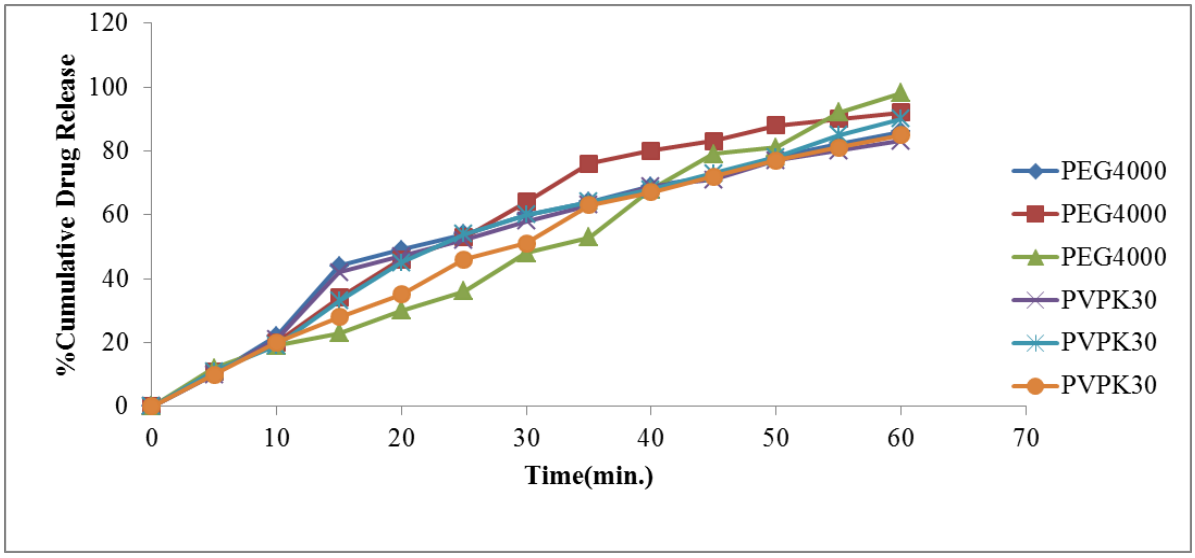

Fig. 3: In-vitro release study of solid dispersion containing drug and carriers for various formulations.

In-vitro dissolution study of solid dispersion

Cumulative drug release were calculated and were compared with the pure drug dissolution and shown in figure 3. All the solid dispersion preparation assure the acceptance level (Q min= 75%), where polyethylene glycol 4000 PEG4000 (1:5) batch display higher protection to drug deterioration in dissolution medium of phosphate buffer PH 7.4.

Drug was up to 78% were feasible in medium of dissolution for the absorption after 40 minutes. From the data of dissolution, it concluded that the PEG4000 (1:5) batch can assure our goal of overcoming the bioavailability variable of Indomethacin (IM). The % cumulative drug releases were match with pure drug, it seen that solubility is increase when it is prepared with solid dispersion.

Pre-compression study of Granules

Table 9: Pre-compression evaluation of prepared Granules of indomethacin.

	Formulation (±SD)					
Parameters	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Bulk density(g/cm³)	0.587±0.044	0.576±0.045	0.579±0.078	0.571±0.072	0.567±0.028	0.560±0.030
Tapped density(g/cm³)	0.665±0.029	0.631±0.045	0.626±0.052	0.634±0.022	0.642±0.062	0.650±0.074
Hausner Ratio	1.13±0.01	1.09±0.02	1.08±0.01	1.11±0.03	1.13±0.05	1.16±0.04
% Carr's compressibility index	11.729±0.002	8.716±0.005	7.507±0.001	9.936±0.004	11.682±0.006	13.846±0.007
Angle of repose(θ)	29±0.28	33±0.78	29±0.30	28±0.71	32±0.45	31±0.02

Post-compression study of matrix tablet of indomethacin

Table 10: Post- compression evaluation of matrix tablets of indomethacin.

Parameters	**Formulations(±SD)**					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Hardness(kg/cm²)	5.23±0.2	5.98±0.1	6.98±0.3	6.12±0.4	6.11±0.5	5.77±0.6
Thickness (mm)	4.79±0.22	4.80±0.20	4.82±0.12	4.78±0.10	4.81±0.13	4.84±0.12
% Friability	0.5±0.1	0.6±0.3	0.8±0.1	0.6±0.3	0.7±0.2	0.9±0.1
% weight Variation (mg)	127.85-135.88	124.65-136.42	129.46-137.47	125.45-136.55	127.64-134.65	131.70-138.65
Drug Content (%w/w)	94.02±0.11	95.08±0.12	98.04±0.09	97.14±0.02	96.18±07	97.04±0.22

Table 11: Drug release studies in 0.1 NHCL.

	Formulation (±SD)					
Time(hrs)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
0.5	2.02±0.35	2.05±0.19	3.77±0.06	2.25±0.36	1.08±0.01	1.29±0.62
1	4.26±0.71	5.49±0.19	6.67±0.11	3.04±0.02	4.98±0.12	3.39±0.13
1.5	7.29±0.45	8.59±0.21	10.32±0.15	7.15±0.73	8.57±0.22	9.88±0.69
2	15.34±0.12	14.87±0.41	18.14±0.18	13.86±0.53	12.60±0.47	16.62±0.24
2.5	22.36±0.21	21.06±0.64	25.46±0.25	19.30±0.58	19.91±0.72	22.33±0.10
3	28.42±0.28	27.76±0.09	32.51±0.28	26.38±0.15	28.41±0.31	29.08±0.18

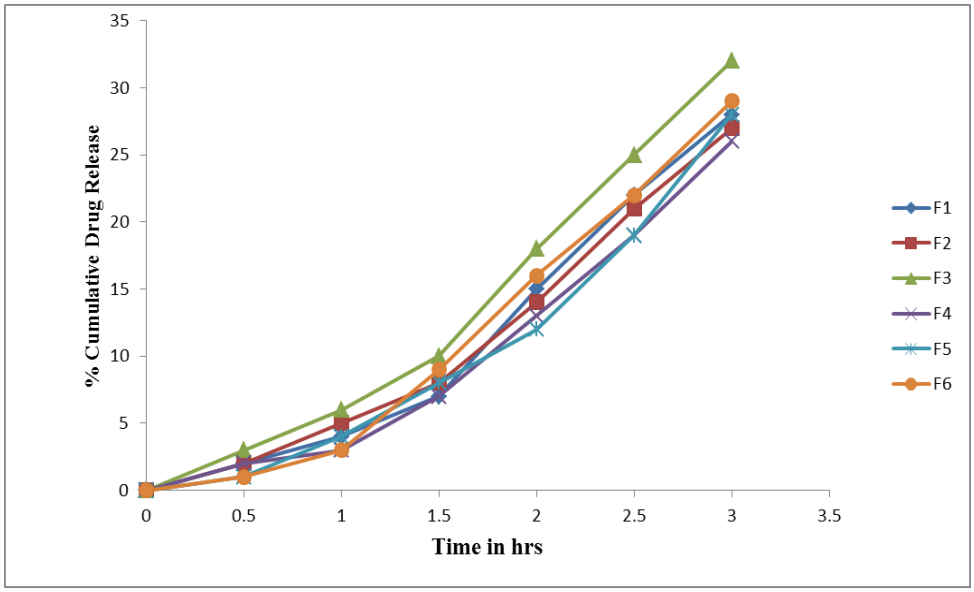

Fig.4: In-vitro drug release profile of all six formulations in 0.1N HCL.

Table 12: Drug release studies in Phosphate buffer pH7.4.

	Formulation (±SD)					
Cumulative %drug released(hrs)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
2	8.22±0.02	11.44±0.25	17.23±0.17	6.90±0.22	7.44±0.18	12.40±0.30
3	12.04±0.11	15.08±0.19	25.94±0.09	10.87±0.35	12.78±0.33	19.14±0.02
5	17.51±0.29	20.43±0.59	30.80±0.20	15.78±0.45	19.55±0.29	25.08±0.05
6	22.65±0.27	27.12±0.61	35.20±0.13	25.68±0.10	31.32±0.39	33.92±0.45
8	28.04±0.40	30.17±0.10	38.07±0.30	32.68±0.39	40.09±0.12	37.09±0.06
10	35.45±0.16	33.49±0.27	44.21±0.40	36.89±0.37	45.56±0.32	48.58±0.42
12	52.11±0.32	48.20±0.20	51.31±0.08	41.32±0.62	56.58±0.38	60.31±0.52
18	66.44±0.12	55.08±0.09	64.42±0.17	56.12±0.60	65.78±0.23	75.23±0.36
24	75.43±0.17	78.47±0.19	83.03±0.12	73.02±0.32	77.99±0.38	80.44±0.18

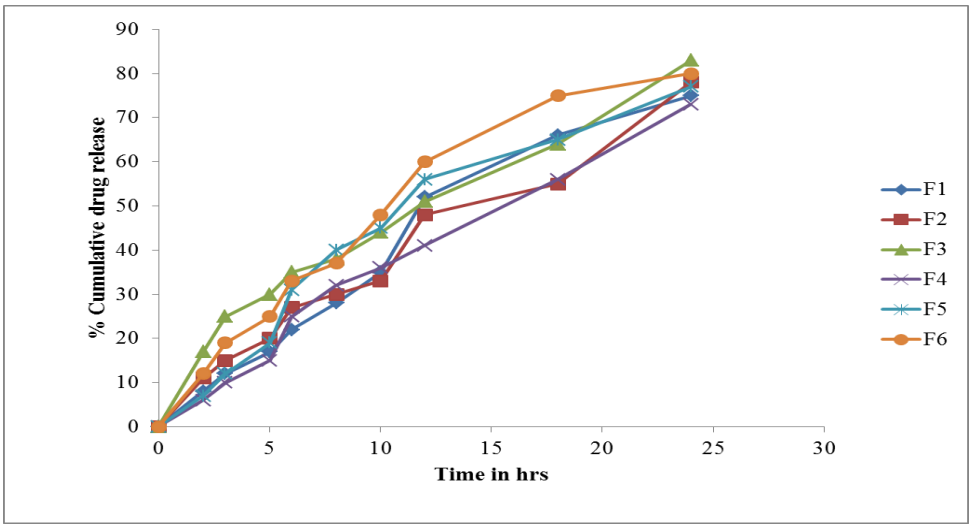

Fig.5: In-vitro drug release profile of all six formulations in Phosphate buffer pH7.4

Stability study

After storage the preparations were analyzed for different parameters, results as shown in table:

Table 13: Stability study of best formulations.

Formulation (±SD)				
Characteristics	**Initial**	**15days**	**30days**	**45days**
Hardness(kg/cm^2)	6.94±0.06	6.85±0.04	6.78±0.11	6.68±0.17
Thickness(mm)	4.81±0.02	4.78±0.08	4.71±0.03	4.65±0.01
%Drug content(w/w)	98.8±0.62	98.6±0.78	98.3±0.62	98.5±0.58
% In vitro drug release	83.3±0.66	83.8±0.55	83.5±0.58	83±0.52
Appearance	White	No change	No change	No Change

CONCLUSION

All the formulations for physical characterization was observed, it shows that all of them comply with the specification of standard reference and official pharmacopoeia. As results of in-vitro dissolution indicates that all batches shows that cumulative release of drug was 75% in 30 minutes drug content results and in-vitro dissolution studies indicates that PEG4000(1:5) batch were having content uniformity(considerable) and dissolution was desirable and also have better solubility. The tablet batches PEG4000 in ratio (1:5) have considerable content of uniformity with better release patterns. Thus, from this discussion it was concluded that PEG4000 enhancing the solubility of Indomethacin as compared to PVPK30 at 1:5 drugs to polymer ratio.

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