CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.7628852

Available online at: http://www.iajps.com *Research Article*

FORMULATION AND OPTIMIZATION OF MOUTH DISSOLVING TABLET CONTAINING INDOMETHACIN SOLID DISPERSION

Chinnam Surekha, Zeenath Ruhy
Mother Teresa College of Pharmacy, Ghatkesar, NFC Nagar, Hyderabad, Telangana,India

Article Received: January 2023 **Accepted:** January 2023 **Published:** February 2023

Abstract:
Indomethacin is a non-steroidal anti-inflammatory drug mainly used for musculo skeletal & joint disorders including ankylosing, spondilitis, osteoarthritis, rhematiod arthiritis acute gout & in inflammation and pain. The major drawback of this drug is its very low water solubility and low erratic absorption from GIT. The purpose of the present investigation was to increase the solubility and dissolution rate of Indomethacin by the preparation of its solid dispersion with polyvinyl pyrrolidone k30, PEG-4000and PEG-6000 using solvent evaporation and physical mixture method and preparation of MDT of indomethacin with different superdisintegrant and sublimable material.Drug polymer interaction were investigated (XRD) and (FTIR). The DSC, XRD and FTIR results showed no drug-polymer chemical interaction in the solid dispersion. Indomethacin solid dispersion with PVP K-30 (1:5) by solvent evaporation was used for the preparation of mouth dissolving tablet with various superdisintegrant by direct compression and sublimation method. The formulated fast dissolving tablets were evaluated for hardness, friability, wetting time, disintegration and in vitro drug released. The hardness of the prepared tablets were found in the range of 2.4 kg/cm2 to 3.2 kg/cm2. The friability values were less than 1%. All the formulation had disintegration time less than 1 min. The formulation SBP3 containing 4% crosspovidone showed 99.93% drug released within 5 min. FT-IR spectra revealed no chemical incompatibility between the drug and PVP K-30. The stability studies were conducted as per ICH guidelines and the formulations were found to be stable with insignificant change in the hardness, disintegration and in vitro drug released pattern.

KEYWORDS: *Indomethacin; Solid dispersion, polyvinyl pyrrolidone K-30; mouth dissolving tablet; superdisintigrants.*

Corresponding author:
Chinnam Surekha,
M. Pharmacy,
Department of Pharmaceutics,
Mother Teresa College of Pharmacy,
Ghatkesar, NFC Nagar, Hyderabad, Telangana
India, E-mail: surekhachinnam98@gmail.com

QR code

Please cite this article in press Chinnam Surekha et al, ***Formulation And Optimization Of Mouth Dissolving Tablet Containing Indomethacin Solid Dispersion.,*** *Indo Am. J. P. Sci, 2023; 10 (02).*

INTRODUCTION:

Over the past three decades Mouth Dissolving Tablets (MDTs) have gained much attention as a preferred alternative to conventional oral dosage forms such as tablets and capsules. An MDT is a solid dosage form that disintegrates and dissolves in the mouth (either on or beneath the tongue or in the buccal cavity) without water within 60 seconds or less and absorption is systemic without first pass metabolism. For people who are having the problem in the swallowing or chewing can take it easily as the disintegrated mass can slide down smoothly with the help of saliva. An MDT is formulated as a bioequivalent line extension of an existing oral dosage form. Superdisintigrants are used for the rapid dissolution and sublimating agents are used to increase porosity. [1-5] he application of an optimization technique consisting of statistical design to pharmaceutical formulation development would provide an efficient and economical method to acquire the necessary information to understand the relationship between controllable (independent)variables and performance or response (dependent)variables [6-9].

Indomethacin is a member of the non-steroidal anti-inflammatory drugs (NSAIDS), chemically [1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-Yl] acetic acid. It is used in musculo skeletal and joint disorders including ankylosing spondylitis, osteoarthritis, rheumatoid arthritis and acute gout and in peri-articular disorder such as buritis and tendinitis may also be used in inflammation, pain and oedema following orthopaedic procedures. The drug is described as practically insoluble and highly permeable (Class-II) drug. Because water insoluble drug often show low absorption and weak bioavailability, improvement in dissolution rate and/or solubility are important for development of drug preparations. The successful formulation of poorly water soluble drugs is one of the major problems in pharmaceutical manufacturing. Indomethacin may show low and erratic oral bioavailability due to poor dissolution of the drug in the fluids of gastrointestinal tract additionally, this undesirable physical property may increase the incidence of irritating side effects on the gastrointestinal tract because of a prolonged contact time with the mucosa. .[10-13]

Therefore in the present study an attempt will be made to formulate mouth dissolving tablets of Indomethacin using superdisintegrants and solid dispersion technique to improve the dissolution rate of this widely used anti rheumatic agent, to obtain more rapid and complete absorption and greater patients compliance.

MATERIALS:

Indomethacin Purchased from SUN pharma. Polyethylene glycol 4000 LR, Polyethylene glycol 6000 LR, Polyvinyl pyrrolidone-K30, Microcrystalline cellulose, Camphor, Magnesium stearate, Lactose from SD fine-chem. Limited, Mumbai.

METHODOLOGY:

Determination of λ_{max} for Indomethacin in phosphate buffer pH (6.8) 100mg of pure drug transferred into 100ml of phosphate buffer pH (6.8) in a volumetric flask. Withdrawn 10ml from this solution and diluted to 100ml it make 100mcg/ml (stock solution) then concentration made by withdrawing 0.5,1, 1.5, 2, 2.5, 3, 3.5 and 4ml from stock solution and diluted to 10ml it makes solution of concentration 5 g/ml, 10 g/ml, 15 g/ml, 20 g/ml, 25 g/ml, 30 g/ml, 35 g/ml, 40 g/ml and sample were scanned between 200-400 nm regions using Shimadzu UV/visible 1700 spectrophotometer; to determine the λ_{max} of Indomethacin in phosphate buffer pH (6.8).

Determination of λ_{max} for Indomethacin in methanol: 100mg of pure drug transferred into 100ml of methanol in a volumetric flask. Withdrawn 10ml from this solution and diluted to 100ml it make 100mcg/ml (stock solution) then diluted to 10ml it makes solution of concentration 5 g/ml, 10 g/ml, 15 g/ml, 20 g/ml, 25 g/ml, 30 g/ml, 35 g/ml, 40 g/ml and sample were scanned between 200-400 nm regions using Shimadzu UV/visible 1700 spectrophotometer; to determine the λ_{max} of Indomethacin in phosphate buffer pH (6.8).

Standard calibration curve of Indomethacin in phosphate buffer pH (6.8)100mg of pure drug transferred into 100ml of phosphate buffer (pH6.8) in a volumetric flask. Withdrawn 10ml from this solution and diluted to 100ml it make 100mcg/ml (stock solution) then concentration made by withdrawing 0.5, 1,1.5, 2, 2.5,3,3.5,4ml from stock solution and diluted to 10ml it makes solution of concentration 5 g/ml, 10 g/ml, 15 g/ml, 20 g/ml , 25 g/ml, 30 g/ml & 40 g/ml.Solution ranging from 5 to 40 g/ml were prepared using phosphate buffer (ph 6.8); separately, absorbance was measured for each solution at λ_{max} of 319nm using Shimadzu UV/visible 1700 spectrophotometer, graph was

plotted for absorbance versus concentration of indomethacin.

Standard calibration curve of Indomethacin in methanol: 100mg of pure drug transferred into 100ml of methanol in a volumetric flask. Withdrawn 1ml from this solution and diluted to 100ml it make 100mcg/ml (stock solution) then concentration made by withdrawing 0.5,1,1.5,2, 2.5,3,3.5, and 4ml from stock solution and diluted to 10ml it makes solution of concentration 5 g/ml, 10 g/ml, 15 g/ml, 20 g/ml , 25 g/ml, 30 g/ml and 40 g/ml. Absorbance was measured for each solution at λ_{max} of 320 nm using Shimadzu UV/visible 1700 spectrophotometer, and graph was plotted for absorbance versus concentration of Indomethacin.

Solvent evaporation method: An accurate amount of Indomethacin and carrier were dissolved in methanol with continuous stirring. The solvent was removed at 40-45c° under vacuum until the solid dispersion was dry. The dried mass was pulverized, passed through 44 mesh sieve and were stored in a desiccator until used for further studies as shown in table**.**

Physical mixture: Physical mixtures were prepared by mixing the calculated amounts of Indomethacin and carriers in a glass mortor by triturating. The resultant solid dispersion was passed through 44 mesh sieve and stored in a dessicator until used for further study as shown in table**.**

Table-1: Formulation of Indomethacin mouth dissolving tablets prepared bydirect compression method (1-tablet)

Ingredients(mg)	DCS1	DCS2	DCS3	DCP1	DCP2	DCP3
Amount of solid dispersionequivalent to 25mg of drug	250	250	250	250	250	250
Lactose mono hydrate	65	61.5	58	65	61.5	58
Sodium starch glycolate	7	10.5	14	-	-	-
Crospovidone	-	-	-	7	10.5	14
Aspartame	3.5	3.5	3.5	3.5	3.5	3.5
Mg stearate	3.5	3.5	3.5	3.5	3.5	3.5
Talc	3.5	3.5	3.5	3.5	3.5	3.5
MCC (Avicel PH-102)	17.5	17.5	17.5	17.5	17.5	17.5
Total	350	350	350	350	350	350

Table-2: Formulation of Indomethacin mouth dissolving tablets prepared by direct compression method (50-tablets)

Ingredients(g)	DCS1	DCS2	DCS3	DCP1	DCP2	DCP3
Amount of solid dispersionequivalent to 25mg of drug	12.500	12.500	12.500	12.500	12.500	12.500
Lactose mono hydrate	3.250	3.075	2.900	3.250	3.075	2.900
Sodium starch glycolate	0.350	0.525	0.700	-	-	-
Crospovidone	-	-	-	0.350	0.525	0.700
Aspartame	0.175	0.175	0.175	0.175	0.175	0.175
Mg stearate	0.175	0.175	0.175	0.175	0.175	0.175
Talc	0.175	0.175	0.175	0.175	0.175	0.175
MCC (Avicel PH-102)	0.875	0.875	0.875	0.875	0.875	0.875

Table-3: Formulation of Indomethacin mouth dissolving tablets prepared bysublimation method (1-tablet)

Ingredients (mg)	SBS1	SBS2	SBS3	SBP1	SBP2	SBP3
Amount of solid dispersionequivalent to 25mg of drug	250	250	250	250	250	250
Lactose mono hydrate	30	26.5	23	30	26.5	23
Sodium starch glycolate	7	10.5	14	-	-	-
Crospovidone	-	-	-	7	10.5	14
Camphor	35	35	35	35	35	35
Aspartame	3.5	3.5	3.5	3.5	3.5	3.5
Mg stearate	3.5	3.5	3.5	3.5	3.5	3.5
Talc	3.5	3.5	3.5	3.5	3.5	3.5
MCC(Avicel PH-102)	17.5	17.5	17.5	17.5	17.5	17.5
Total	350	350	350	350	350	350

Table-4: Formulation of Indomethacin mouth dissolving tablets prepared bysublimation method (50-tablets)

Ingredients(g)	SBS1	SBS2	SBS3	SBP1	SBP2	SBP3
Amount of solid dispersionequivalent to 25mg of drug	12.500	12.500	12.500	12.500	12.500	12.500
Lactose mono hydrate	1.500	1.325	1.150	1.500	1.325	1.150
Sodium starch glycolate	0.350	0.525	0.700	-	-	-
Crospovidone	-	-	-	0.350	0.525	0.700
Camphor	1.750	1.750	1.750	1.750	1.750	1.750
Aspartame	0.175	0.175	0.175	0.175	0.175	0.175
Mg stearate	0.175	0.175	0.175	0.175	0.175	0.175
Talc	0.175	0.175	0.175	0.175	0.175	0.175
MCC(Avicel PH-102)	0.875	0.875	0.875	0.875	0.875	0.875
Total	17.500	17.500	17.500	17.500	17.500	17.500

RESULTS AND DISCUSSION:

Table 5: Standard calibration data of Indomethacin in pH

6.8 phosphate buffer at 319 nm

Sr. No.	Concentration(mcg/ml)	Absorbance*(nm) SD
1	00	0.000
2	05	0.092
3	10	0.197
4	15	0.288
5	20	0.401
6	25	0.488
7	30	0.590
8	35	0.680
9	40	0.774

*Average of three determinations

Figure-1: Standard calibration curve of Indomethacin in pH 6.8 phosphate bufferat 319 nm

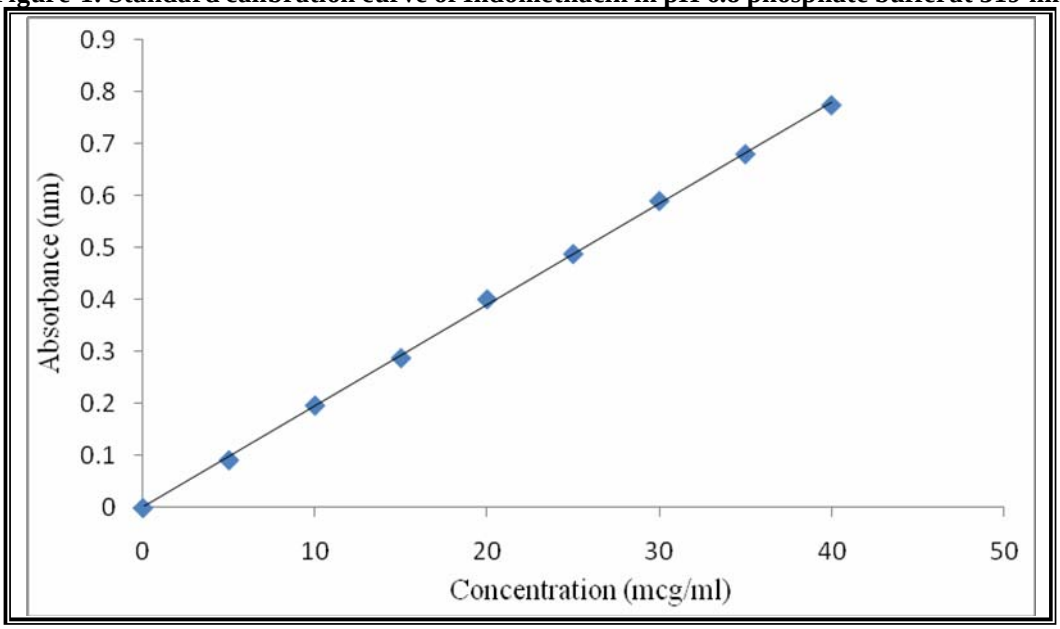


Table-6: Standard calibration data of Indomethacin in Methanol at 320 nm

Sr. No.	Concentration (mcg/ml)	Absorbance*(nm) SD
1	00	0.000
2	05	0.092
3	10	0.192
4	15	0.287
5	20	0.364
6	25	0.452
7	30	0.549
8	35	0.644
9	40	0.745

*Average of three determinations

Figure-2: Standard calibration curve of Indomethacin in Methanol at 320nm

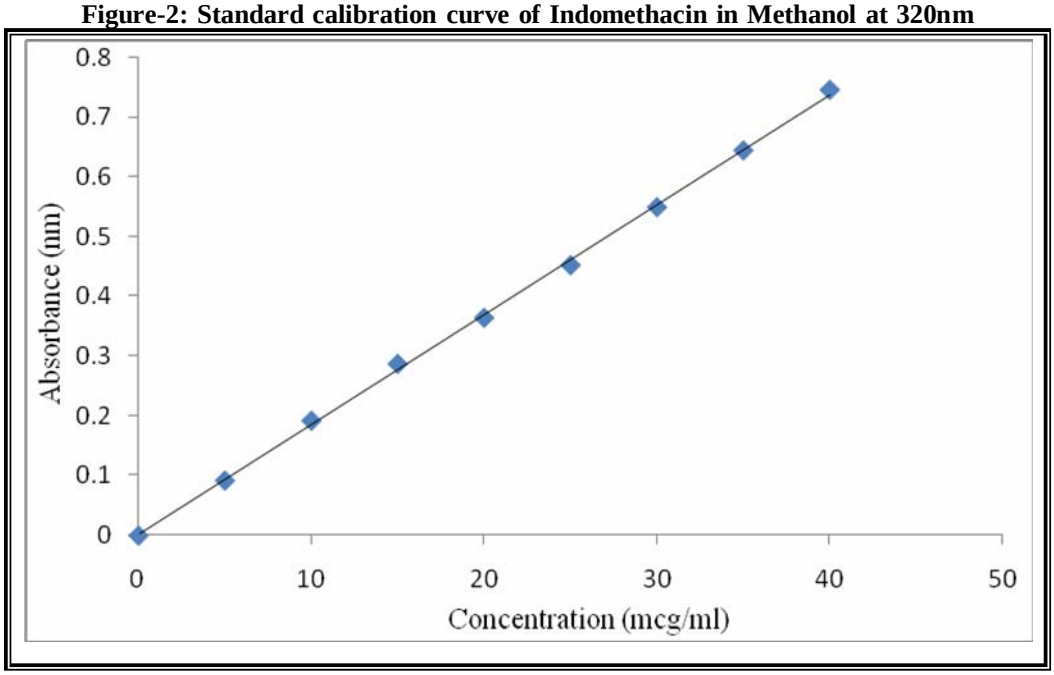
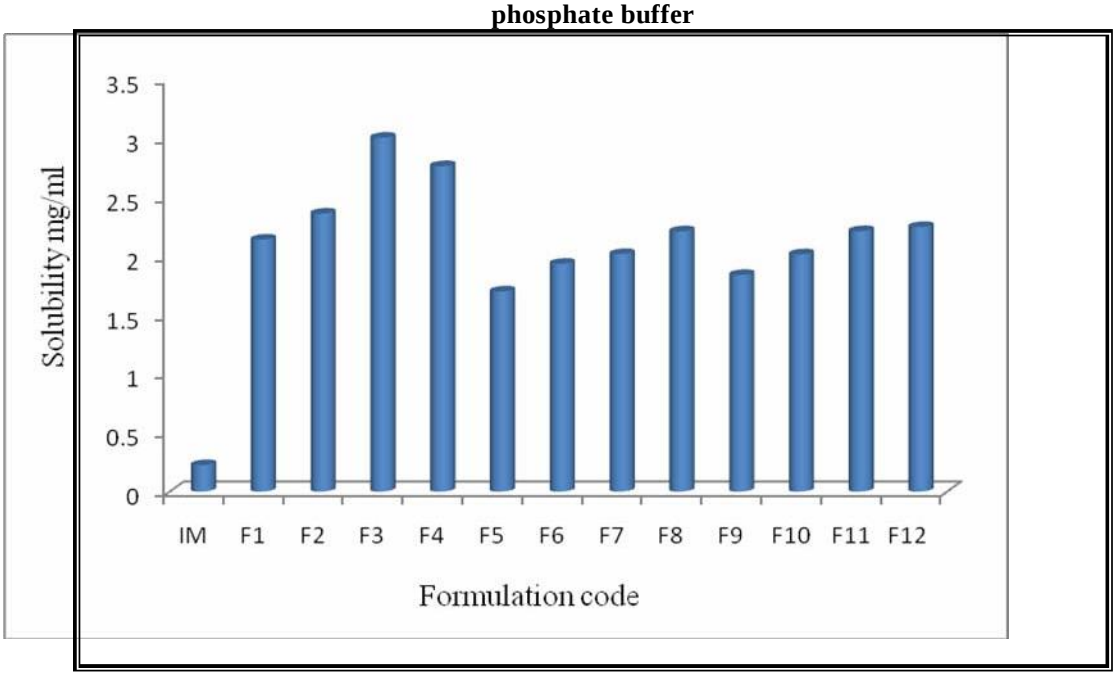


Table-7: Percentage practical yield, drug content uniformity and phasesolubility studies and of Indomethacin solid dispersion

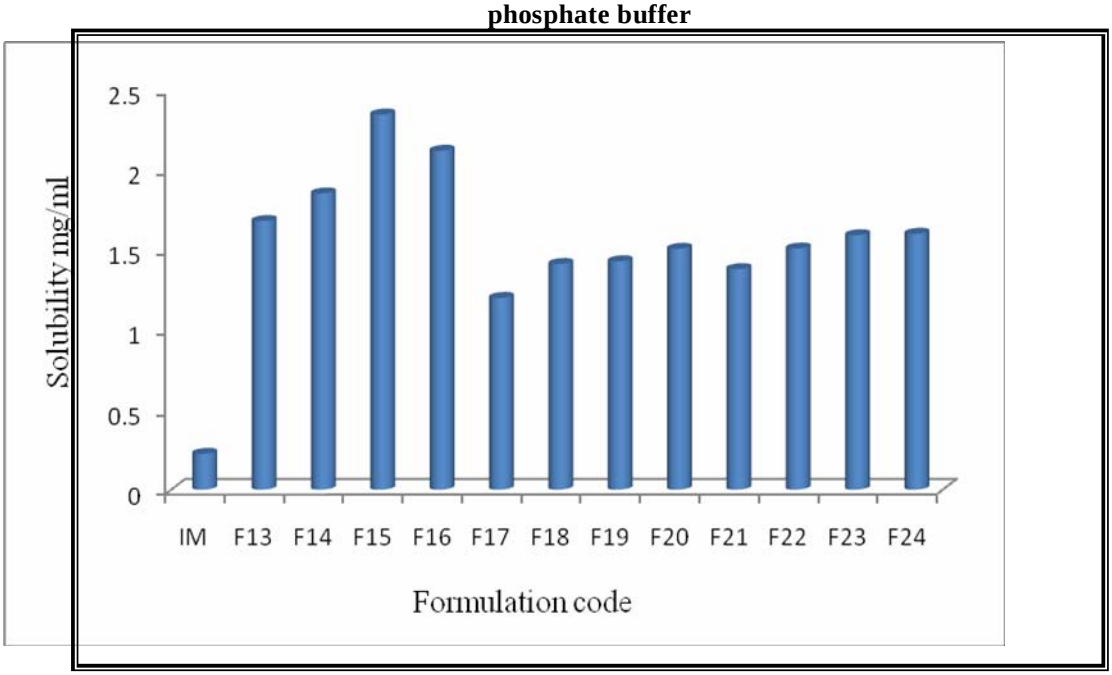
FormulationCode	% PracticalYield	Drug Content Uniformity* (%) SD	Solubility in 6.8Phosphate Buffer* (g/ml) SD
IM	-	-	0.224
F1	97.25	98.12	2.139
F2	98.00	97.28	2.360
F3	98.95	100.73	3.004
F4	97.13	99.32	2.763
F5	89.80	96.66	1.699
F6	90.70	98.64	1.934
F7	88.00	98.35	2.016
F8	87.12	97.63	2.209
F9	93.00	97.26	1.839
F10	91.00	94.34	2.014
F11	94.15	98.52	2.211
F12	93.45	97.84	2.246
F13	98.12	96.08	1.680
F14	98.00	95.43	1.852
F15	98.24	96.82	2.346
F16	97.74	97.25	2.119
F17	98.12	93.78	1.199
F18	98.00	95.37	1.411
F19	97.13	96.54	1.428
F20	97.00	94.49	1.506
F21	98.18	95.47	1.379
F22	98.65	95.08	1.508
F23	97.62	95.53	1.591
F24	97.50	95.60	1.601

*Average of three determinations

Figuer-3: Solubility study of Indomethacin solid dispersion prepared bysolvent evaporation method in 6.8 phosphate buffer



Figuer-4: Solubility study of Indomethacin solid dispersion prepared byphysical mixture method in 6.8 phosphate buffer



5.1 DISSOLUTION STUDY:

Table-8: Dissolution profile of Indomethacin from (F1, F2, F3 and F4) soliddispersion

Time(min)	Cumulative % drug released* SD				
	IM	F1	F2	F3	F4
0	0.00	0.00	0.00	0.00	0.00
15	1.79±0.32	16.99± 0.35	23.76±0.77	36.8±0.33	29.86± 0.07
30	2.87± 0.38	29.81± 0.66	34.65±0.31	54.1± 0.46	44.71± 0.11
45	4.48± 0.45	49.43± 0.75	52.01±0.13	66.07±0.64	56.43± 0.18
60	6.28± 0.78	60.21± 0.65	64.44±0.61	70.74± 0.68	67.45± 0.81
90	9.51± 0.05	79.78± 0.03	83.07± 0.91	83.19± 0.86	83.99± 0.96
120	13.64± 0.16	85.94± 0.14	87.92± 0.97	91.03±0.98	90.67± 0.69
150	17.23± 0.50	90.97± 0.41	93.01± 0.79	95.04± 0.89	95.46± 0.87
180	21.01± 0.92	96.29± 0.99	97.31± 0.17	99.59±0.09	98.09± 0.20

* Average of three determinations

Figure-5: Release profile of Indomethacin from (F1, F2, F3 and F4) Soliddispersion

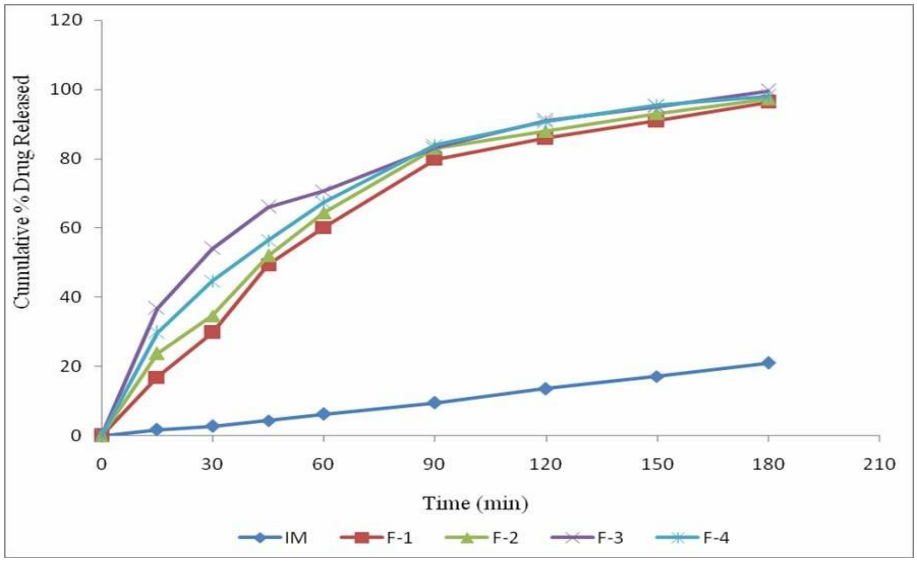


Table-9: Dissolution profile of Indomethacin from (F5, F6, F7 and F8) soliddispersion

Time(min)	Cumulative % drug released* SD				
	IM	F5	F6	F7	F8
0	0.00	0.00	0.00	0.00	0.00
15	1.79± 0.077	22.62± 0.38	19.75±0.66	23.94± 0.77	29.88± 0.72
30	2.87± 0.13	34.68± 0.78	29.92±0.65	34.77± 0.37	39.14± 0.62
45	4.48± 0.91	43.93± 0.16	44.82± 0.14	47.76± 0.12	50.87± 0.06
60	6.28± 0.79	48.83± 0.92	56.91± 0.99	62.36± 0.84	63.80± 0.19
90	9.51± 0.31	59.91± 0.32	68.16± 0.35	72.77±0. 94	72.77± 0.9
120	13.64± 0.61	66.27± 0.45	72.29± 0.75	79.12± 0.76	81.21± 0.20
150	17.23± 0.97	74.63± 0.05	79.54± 0.14	86.84± 0.85	88.75± 0.25
180	21.01± 0.71	86.24± 0.50	88.81± 0.98	90.37± 0.80	92.46± 0.52

*Average of three determinations

Figure-6: Release profile of Indomethacin from (F5, F6, F7 and F8) Soliddispersion:

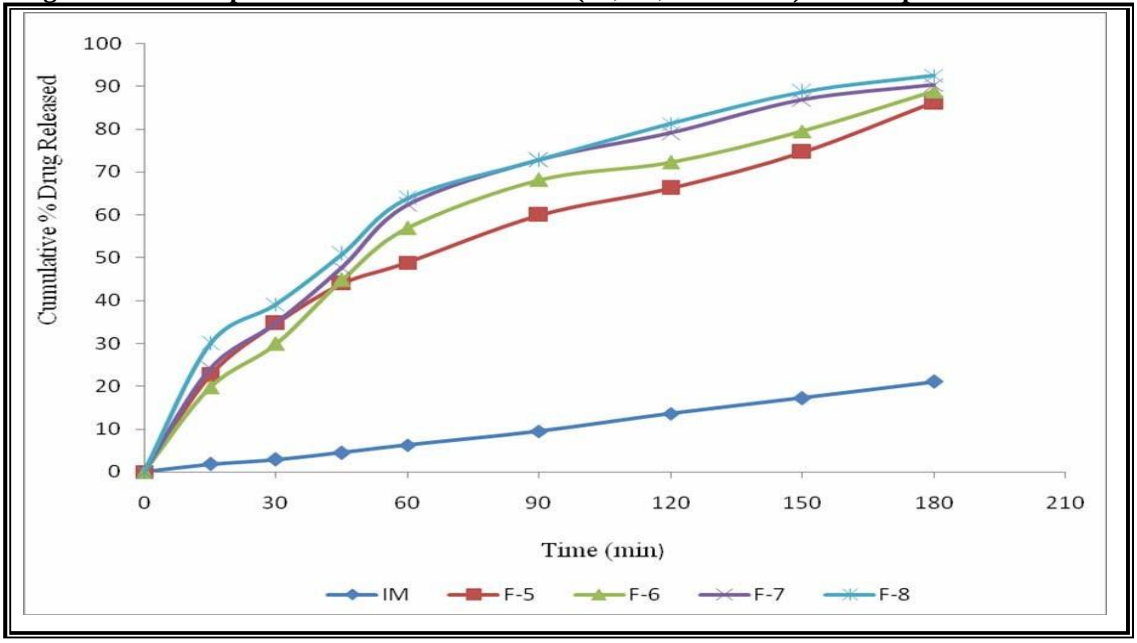


Table-10: Dissolution profile of Indomethacin from (F9, F10, F11 and F12) solid dispersion

Time(min)	Cumulative % drug released* SD				
	IM	F9	F10	F11	F12
0	0.00	0.00	0.00	0.00	0.00
15	1.79 ± 0.18	20.10±0.85	14.9± 0.79	26.93±0.56	31.12±0.88
30	2.87 ± 0.22	34.83±0.93	27.65± 0.24	38.91±0.44	41.71±0.74
45	4.48 ± 0.36	45.42±0.12	41.47± 0.18	50.81±0.72	65.65±0.32
60	6. 28 ± 0.25	60.92±0.24	55.83± 0.67	63.48±0.23	70.86±0.54
90	9.51 ± 0.76	66.72±0.66	66.55± 0.44	78.64±0.70	77.98±0.38
120	13.64 ± 0.45	72.77±0.42	74.36± 0.35	84.62±0.88	88.81±0.76
150	17.23 ± 0.19	81.83±0.30	85.22± 0.25	93.91±0.56	94.56±0.18
180	21.01 ± 0.77	93.31±0.05	95.34± 019	97.25±052	99.10±0.41

*Average of three determinations

Figure-7: Release profile of Indomethacin from (F9, F10, F11 and F12) Soliddispersion

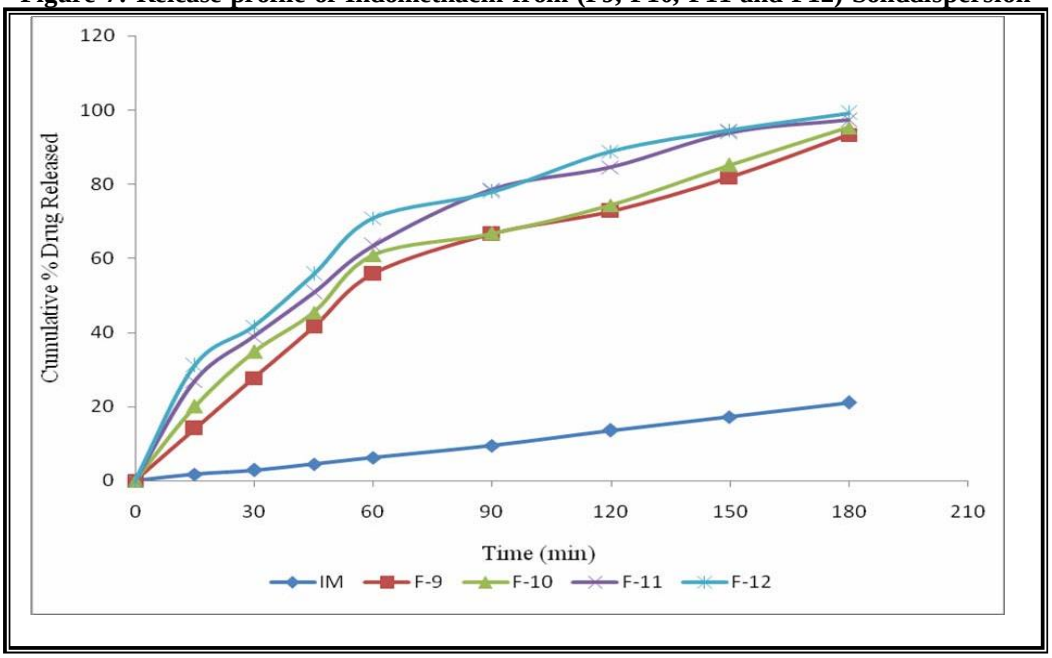


Table-11: Dissolution profile of Indomethacin from (F13, F14, F15 and F16) solid dispersion

Time(min)	Cumulative % drug released* SD				
	IM	F13	F14	F15	F16
0	0.00	0.00	0.00	0.00	0.00
15	1.79± 0.23	14.9±0.55	19.09± 0.65	24.47± 0.51	26.15± 0.56
30	2.87± 0.32	26.99±0.42	29.68± 0.34	34.66± 0.65	38.01± 0.45
45	4.48± 0.25	46.74±0.78	44.22± 0.39	50.15±0.92	54.34± 0.30
60	6.28± 0.52	56.49±0.32	60.02± 0.93	66.13±0.28	68.88± 0.95
90	9.51± 0.70	70.86±0.45	76.75± 0.87	79.43± 0.83	74.75± 0.59
120	13.64± 0.6	82.05±0.17	85.72± 0.09	86.92± 0.97	83.15± 0.81
150	17.23± 0.12	86.61± 0.61	88.15± 0.5	90.73± 0.67	92.22± 0.12
180	21.01± 0.33	93.91± 0.21	95.04± 0.16	96.01± 0.72	97.07± 0.19

*Average of three determinations

Figure-8: Release profile of Indomethacin from (F13, F14, F15 and F16)Solid dispersion

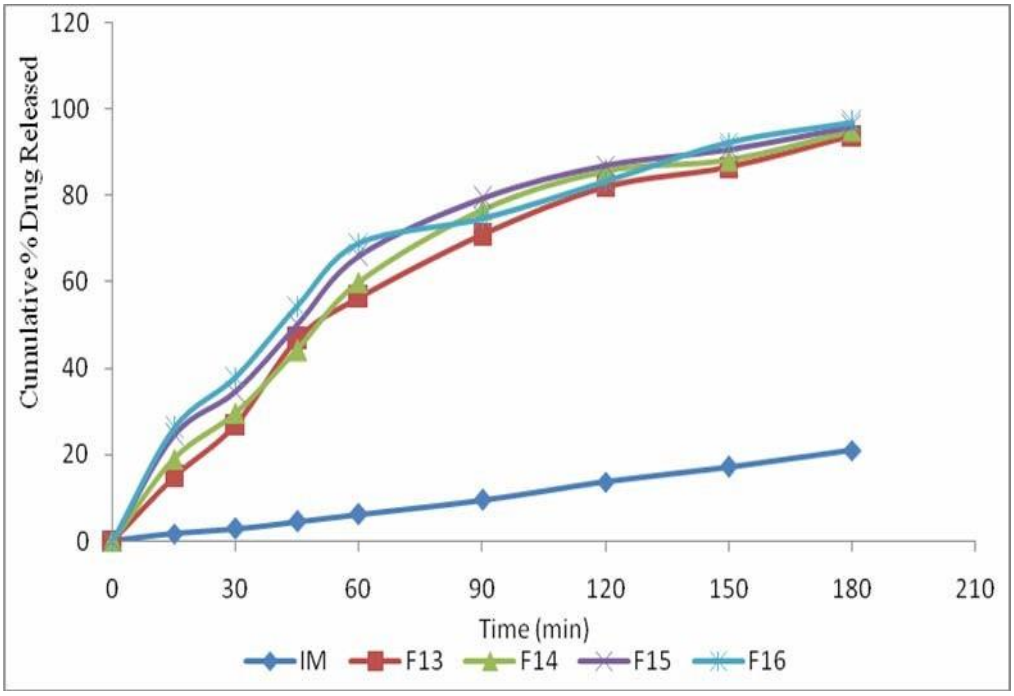


Table-12: Dissolution profile of Indomethacin from (F17, F18, F19 and F20) solid dispersion

Time(min)	Cumulative % drug released* SD				
	IM	F17	F18	F19	F20
0	0.00	0.00	0.00	0.00	0.00
15	1.79± 0.80	10.95±0.43	13.78±0.42	16.81± 0.14	21.01±0.49
30	2.87± 0 81	20.34±0.76	23.71±0.53	28.84± 0.06	32.79±0.93
45	4.48± 0 62	34.96±0.67	38.72±0.20	44.71± 0.12	46.98±0.55
60	6.28± 0 62	43.63±0.89	50.87±0.99	57.99± 0.21	58.82±0.94
90	9.51± 0.76	56.79±0.56	62.61±0.87	64.99± 0.30	67.51±0.96
120	13.64± 0.79	65.88±0.90	69.48±0.66	72.65± 0.69	76.24±0.44
150	17.23± 0.87	74.69±0.84	78.52±0.88	80.73± 0.82	80.49±0.20
180	21.01±0.54	83.85±0.75	86.42±0.05	87.98± 0.70	92.28±0.10

*Average of three determinations

Figure-9: Release profile of Indomethacin from (F17, F18, F19 and F20)Solid dispersion

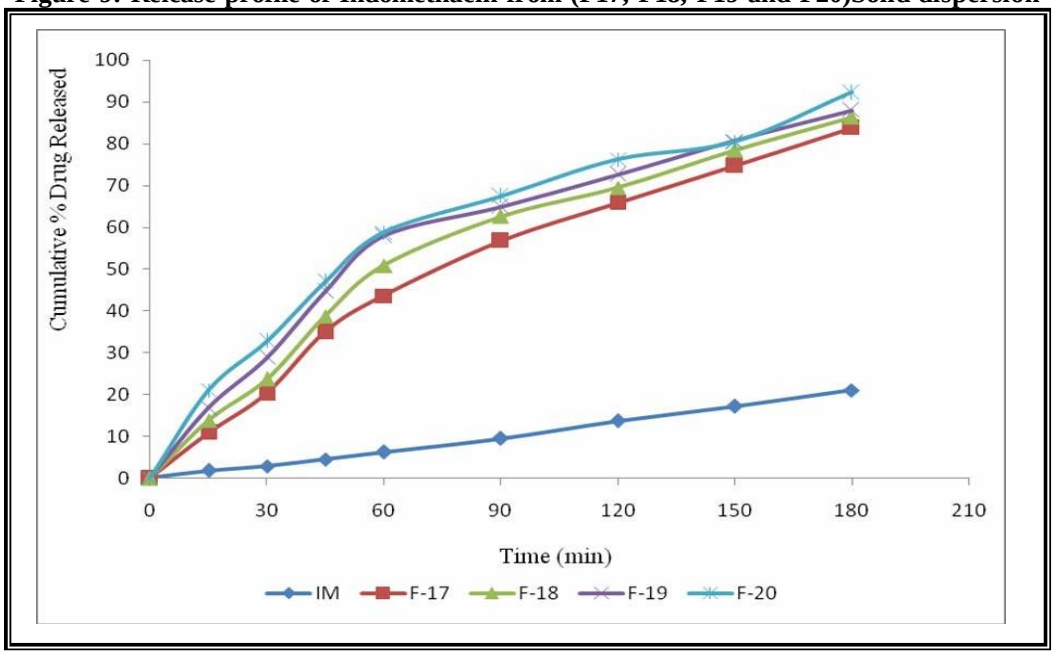
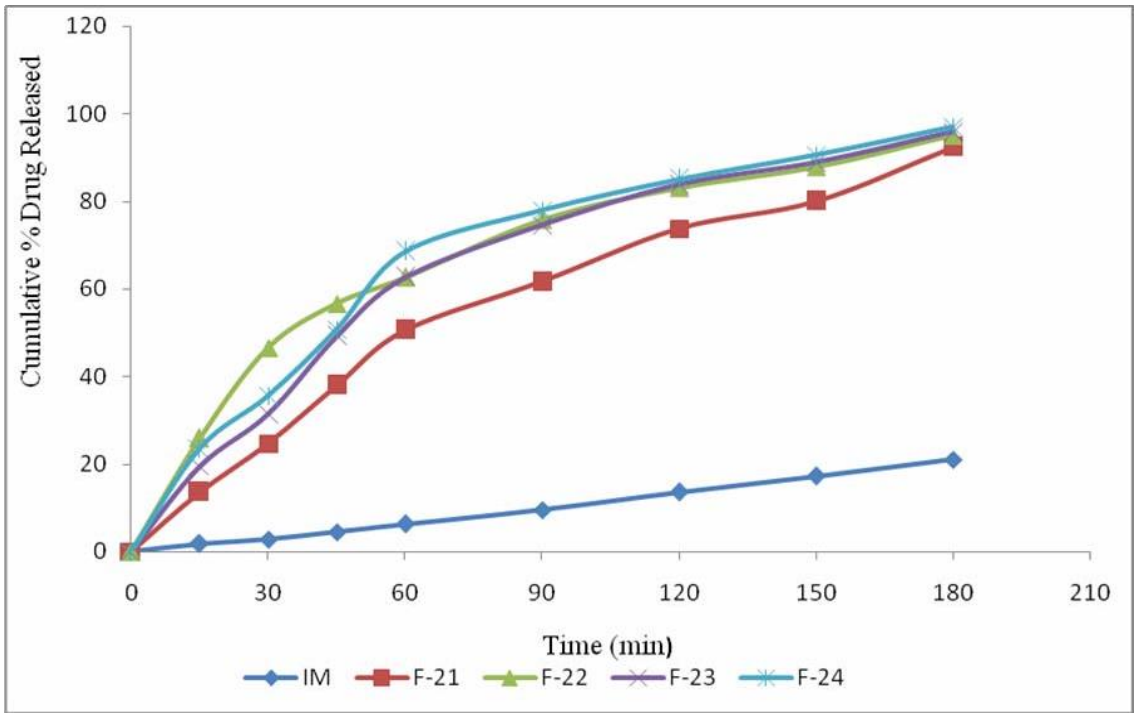


Table-13: Dissolution profile of Indomethacin from (F21, F22, F23, F24) soliddispersion

Time(min)	Cumulative % drug released* SD				
	IM	F21	F22	F23	F24
0	0.00	0.00	0.00	0.00	0.00
15	1.79±0 .88	13.64± 0.54	25.97± 0.63	19.51± 0.10	23.58± 0.07
30	2.87±0 .67	24.71± 0.98	46.62± 0.26	31.42± 0.27	35.61± 0.28
45	4.48±0 .43	37.94± 0.74	56.66± 0.89	49.25± 0.44	50.75± 0.44
60	6.28±0. 86	50.69± 0.65	62.63± 0.75	62.71± 0.96	68.58± 0.77
90	9.51±0 .92	61.64± 0.32	5.91± 0.98	74.63± 0.53	77.92± 0.91
120	13.64± 0.77	73.79± 0.12	83.13± 0.81	83.79± 0.69	85.1± 0.21
150	17.23± 0.45	80.01± 0.05	87.92± 0.16	88.87± 0.91	90.55± 0.39
180	21.01± 0.55	92.34± 0.16	95.04± 0.09	95.94± 0.01	97.01± 0.87

*Average of three determinations

Figure-10: Release profile of Indomethacin from (F21, F22, F23 and F24)Solid dispersion



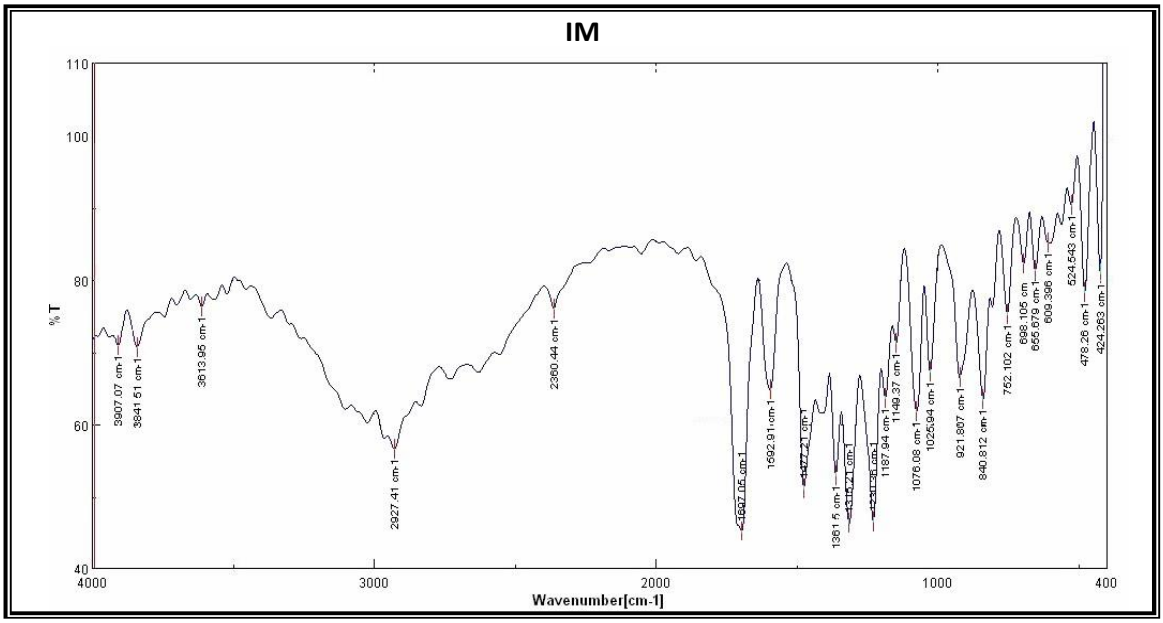
EVALUATION OF SOLID DISPERSION INCORPORATEDINDOMETHACIN MOUTH DISSOLVING TABLET

Table-14: Results of pre-compression parameter for tablet prepared by direct Compression technique:

Formulationcode	Bulk density * (g/cc) SD	Tapped density*(g/cc) SD	Angle of repose* (degree) SD	Carr'sindex* (%) SD	Hausner's Ratio* SD
PF	0.575±0.89	0.853±0.78	34.65±0.43	17.94±0.74	1.48±0.67
DCS1	0.575±0.67	0.851±0.65	37.53±0.70	17.94±0.36	1.48±0.87
DSC2	0.579±0.54	0.845±0.89	35.92±0.13	16.14±0.65	1.45±0.25
DCS3	0.579±0.32	0.850±0.56	36.46±0.31	17.94±0.73	1.46±0.19
DCP1	0.577±0.21	0.855±0.16	32.67±0.54	17.94±0.37	1.48±0.11
DCP2	0.579±0.29	0.842±0.76	35.09±0.78	16.14±0.62	1.45±0.04
DCP3	0.572±0.90	0.843±0.55	32.50±0.66	16.14±0.40	1.47±0.94

*Average of three determinations

Figure 11: IR Spectra of pure drug (IM)



DISCUSSION:

In the present investigation, an attempt were made to improve the solubility and dissolution rate of a poorly water soluble drug, Indomethacin by solid dispersion method using PVP-K30, polyethylene glycol (PEG) 4000 and polyethylene glycol (PEG) 6000 as carrier. Solid dispersion of Indomethacin was prepared by physical mixture and solvent evaporation method. The prepared solid dispersion was evaluated for number of parameters like percent practical yield, drug content uniformity studies, Solubility studies and *in- vitro* drug release studies and FTIR, DSC and XRD etc.

Percent Practical yield:

Solid dispersions of Indomethacin were prepared by different method using carriers like PVP-K30, and PEG-4000, PEG-6000. In the present work, total 24 formulations were prepared and their complete composition is shown in Table.Solid dispersion prepared by two technique i.e., solvent evaporation method and physical mixture. The solid dispersion of PVP-K30 prepared by solvent evaporation method was light yellow colour fine powder and solid dispersion of PEG-4000 and PEG-6000 was white creamy colour powder. The solid dispersionof PVP-K30, PEG-4000 and PEG-6000 prepared by physical mixture was white fine powders. The % Practical yield of the prepared solid dispersions was found to be in the range of 87.12 – 98.95. The maximum yield was found to be 98.95% in F3.

Content Uniformity Studies:

The actual drug content of all the 24 formulations. The drug content of the prepared solid dispersions was found to be in the range of 93.78-100.73% indicating the application of the present methods for the preparation of Solid dispersions with high content uniformity. The maximum % drug content was found to be 100.73% in F3.

Phase solubility study:

The solubility study was carried out in pH 6.8 phosphate buffer. The solubility of pure Indomethacin was less as compared to its solid dispersion. The solubility of Indomethacin was increased by using different carrier (PVP-K30, PEG-4000 and PEG-6000). The maximum solubility was seen with F3 formulation which was prepared by using Indomethacin:(PVP-K30) in 1.5 by solvent evaporation method.

In vitro Dissolution study:

All Indomethacin solid dispersions and pure drug were subjected to in vitro dissolution study in pH 6.8 phosphate buffer. It was found that the dissolution of solid dispersion from all the formulation was more than 83.85% within 180 minutes as compared to pure Indomethacin which shows only 21.01% of drug release. The highest percent drug dissolution was observed with PVP-K30 solid dispersion in ratio 1:5 (F3) (99.59%) as compared to PEG-4000 and PE-G600. The *in vitro* drug release was increased in the manner of pure drug <PEG-4000< PEG-6000< PVP-K30. The results of *in vitro* dissolution study were correlated with the solubility study. The results were inconsistent with the previous reports.

Infrared spectroscopy (IR)

The drug Indomethacin is a taken for preparation of various formulation using different polymer at varying concentration. The IR spectrum of the drug indicatedthe presence of aromatic and aliphatic C-H, absorption peak from 3042, 2927 cm A carboxylic acid carbonyl peak absorption C=O of amide have merged to give rise to a broad peak at 1697 cm indicating the presence of those functionality in adrug molecules.

F3 The first polymer taken for the formulation process drug Indomathacin and PVP- K30. This polymer showed the absence of aromatic C-H peak. Suggesting that this polymer is not aromatic in nature however C=O of the cyclic amid indicate its presence by exhibiting peak at 1720 cm suggesting that a it is a five member ring cyclic molecule. When IR spectrum of the formulation a recording all the functional group absorption of Indomethacin as well as PVP-K30 have remain un effected indicating that during the formulation process drug has not under gone any chemical reaction with the polymer . The formulation product obtained is nothing but mixture of this compound in an unreacted form. This factor supposesthe idea of the drug is present in the formulation in the free form and available forany biochemical properties.

F8 The above drug Indomethacin is taken for second formulation process using polymer PEG-4000. The PEG-4000 exhibited to strong peaks at 3403 cm, 3370 cm indicating the presence of hydroxyl groups in the molecule number absorption peaks are found to be present in the C=O absorption range and also not of the aromatic C-H absorption peaks are notice above 3000 cm. This spectral absorption data are in confirmative with the structure of PEG-4000. The formulation is obtained with Indomethacin and PEG-4000. The IR spectrum it was obtain it is found that neither chemistric peaks of drug and polymer are the

distarted in the IR spectrum of the formulation suggesting that formulated product obtain in this case is also a mixture of drug and the polymer but not the reaction product. Hence drug present In the formulation is in the free form.

F12 In the next formulation drug Indomethacin is taken along with PEG-6000 for formulation process. The characteristic absorption PEG-6000 is almost identical with characteristic absorption PEG-6000 is almost identical with the characteristic absorption peak of PEG-4000. The formulation product obtain is taken for IR recording which shows all the characteristic absorption peaks of drug as well polymer PEG-6000 suggesting that in this case also the mixture of the drug Indomethacin and polymer PEG-6000 obtain no chemical reaction has taken place between this two molecule. During the process of formulation. Hence observation strongly suggests that the drug present in the formula has remained in unreactant form.

F24 Little change in the formulation process has been carried out by physical mixing drug Indomethacin with the polymer PEG-6000. The IR spectrum of such formulation also exhibited identical spectrum with the previous formulation process using this two

In all the above cases when ever formulation is carried out using drug and polymers physical mixture are obtain but not the reaction products. Suggesting that in all the cases formulation obtained contain drug in the free form and available form any biochemical process.

Differential scanning calorimetry (DSC):

IM The drug Indomthacin and formulation obtain during present investigation are subjected for (DSC process) drug Indomethacin has started melting process at

160.4 c this short melting process suggest that drug is in its pure form exhibits short melting range.

F3 When the formulation is prepared using drug Indomethacin and polymer PVP- K30 this formulation product when taken for DSC measurement. The mixture starts melting at 52.9 ^{0}C and completes at 113.2 ^{0}C suggestive that the formulated product is a mixture of this two molecule. Suppose it would have been reaction product. The product should have given narrow range of melting process. But in this case it starts 52.9 ^{0}C and completes at 113.2 ^{0}C supporting the idea that formulation is a mixture of drug and polymer.

F8 In case of second formulation the drug Indomethacin is taken with PEG-4000 in this case also wide range of melting process was notice which sets at 53.5 ^{0}C and completes at 61.05 ^{0}C supporting the idea that formulation obtain in this process is a mixture of drug and the polymer but not the reaction product of drug and polymer.

F12 During next formulation process DSC exhibited 3 different readings in the first place the mixture start melting at 57.0 ^{0}C and complete at 65.05 ^{0}C. The second Case sets at 159.5 ^{0}C and complete at 187.11 ^{0}C and third point which sets at 220.9 c completes at 231.09 ^{0}C this observation suggest that during the formulation process the constituent are existing independently and have not under gone any chemical reaction to give a single reaction product. Hence in this case the formulation obtains at the physical mixture but not the reacted product.

F24 In forth formulation process the drug Indomethacin is mixed with PEG-6000 physically suggesting that physical mixing process as also not under gone any chemical reaction to give rise to reacted product this formulation start melting at

56.3 ^{0}C and complete at 65.07 ^{0}C suggesting that all the formulation product obtain in four case and all physically mixture.

Powder X-Ray Diffractometry (PXRD):

Crystallinity has a great impact on the solubility and dissolution rate of poorly water-soluble drugs. It reflects the characteristic fingerprint region in the sample. Due to this specificity of the fingerprint, crystallinity in the drug can be separately identified from crystallinity in the carrier. Hence, PXRD which is useful tool for the detection of crystallinity in powder micro crystalline states was used to characterize the indomethacin solid dispersion system. The XRD pattern of pure indomethacin showed various diffraction peaks that were intense and sharp; indicating its crystalline nature. The spectrum of PVP-K30, PEG-4000, and PEG600 was characterized by the complete absence of any diffraction peak.

The diffraction pattern of physical mixture showed –few principle peaks of indomethacin with significant decrease in the intensity of peak indicating the reduction in crystallinity. However in solid dispersion system prepaid with PEG- 4000, and PEG600 by solvent evaporation method, the crystallinity of indomethacin was found to be reduced to a greater extent, evidenced by marked reduction in the number as well as the intensity of peaks. The XRD pattern of solid dispersion

systems prepared with PVP-K30 by solvent evaporation methodshows complete disappearance of intense peaks suggested amorphization of indomethacin.

Solid dispersion containing Indomethacin: PVP-K30 (1:5) by Solventevaporation method. (F3) was chosen as best formulation and mouth dissolving tablet of indomethacin were prepared. Moth dissolving tablet prepared by direct compression and sblimation using super disintegration such as sodium starch glycolate and crospovidone in sublimation technique.Campor is used as subliming agent

Before preparation of tablets pre compression parameters of the powderedblend such as Angle of repose, Bulk density, Tapped density, Hausner ration, Compressibility index (%), and drug polymer interaction were studied. Then post compression parameter of tablet such as Hardness, Friability, Weight variation, Uniformity of thickness, Drug content uniformity, Wetting time, In vitro disintegration time, In vitro dissolution studies, FTIR and Stability studies were studied.

Parameter for tablet prepared by direct compression and sublimation methods:

Pre-compression parameters: Powder ready for compression containing drug and various excipients were subjected for pre-compression parameters (Micromeritic properties) to study the flow properties of powder, to achieve uniformity of tablet weight. The results of all the preformulation parameters are given tables no 24 and 25.

Angle of repose (θ):

The data obtained from angle of repose for all the formulations were foundto be in the range of $32^0.50`$ and $37^0.53`$. All the formulations prepared by both the methods showed the angle of repose less than 40^0, which reveals Passableproperty. As mentioned earlier in the literature

Bulk density:

Loose bulk density (LBD) and tapped bulk density (TBD) for the blend was performed. The loose bulk density and tapped bulk density for the entire formulation blend varied from 0.572 gm/cm^3 to 0.579 gm/cm^3 (direct compression and sublimation method) respectively and tapped density for the entire formulation blend varied from 0.842 gm/cm^3 to 0.855 gm/cm^3 (direct compression and sublimation method) respectively.

Carr's consolidation index:

The results of Carr's consolidation index or compressibility index (%) forthe entire formulation blend ranged from 16.14% to 17.94%. The directly compressible powdered had shown excellent compressibility index values up to 15% result in poor flow properties[65].

Hausner ratio:

Hausner ratio of entire formulation showed between 1.45 to 1.48 indicates better flow properties.

Post-compressional tablets prepared by direct compression and sublimation methods:

Hardness:

The hardness of all the tablets prepared by direct compresion methods was found within the 2.4 kg/cm^2 to 3.2 kg/cm^2.

Friability test:

The friability was found in all designed formulations in the range 0.44 to 0.78% to be well within the approved range (<1%).

Thickness:

The mean thickness was (n=3) almost uniform in all the formulations and values ranged from 5.84±0.76 mm to 5.87 ± 0.54 mm. The standard deviation values indicated that all the formulations were within the range.

Weight variation test:

The weight variation was found in all designed formulations in the range 340 to 354 mg.

All the tablets passed weight variation test as the average percentage weight variation was within 5% i.e. in the pharmacopeial limits.

In vitro disintegration time:

The tablets were also evaluated for in vitro disintegration time and 27.The tablet prepared by direct compression method of batch 10 and 12 undergoes *invitro* disintegration time within 21 and 53 seconds. The tablets of the same composition were prepared by sublimation method and that disintegrtes with 14 & 49 seconds respectively.

Wetting time:

Wetting time is closely related to the inner structure of the tablet. The wetting time of Indomethacin tablets prepared by direct compression and sublimation method were found to be in the range of 12 to 41 sec. Promising formulations DCP2 (3%Crospovidon) and SBP3 (4% Crospovidone) showed a wetting time of 14

and 12 sec respectively, which facilitate the faster dispersion in the mouth.

Drug Content:

The drug content uniformity was performed for all the 12 formulations and results are tabulated in table. Three trials from each batch were analyzed spectrophotometrically. The average value and standard deviations of all the formulations were calculated. The percentage drugs content of the tablets were found to be between 98.16 1.07 %to 99.72 0.98 % of Indomethacin. The results were within the range and that indicated uniformity of mixing.

***In vitro* dissolution studies:**

Dissolution rate was studied by using USP type-II apparatus (USP XXIII Dissolution Test Apparatus at 50 rpm) using 900ml of phosphate buffer pH (6.8) as dissolution medium. Temperature of the dissolution medium was maintained at 37 0.5°C, aliquot of dissolution medium was withdrawn at every 1 minute interval and filtered. The absorbance of filtered solution was measured by UV spectrophotometric method at 319nm and concentration of the drug was determined from standard calibration curve.

The tablets prepared by direct compression method employing Sodium starch glycolate as the superdisintegrant released 98.93% to 99.00% of the drug in 11minutes were as the tablets prepared by using crospovidone have released 98.75% to 99.50% of drug in 10 minutes were shown in the table-28.The tablet prepared by sublimation method with Sodium starch glycolate as the superdisintegrants released 98.93% to 99.65% of the drug in 9 minutes. were as the tablets prepared by using crospovidone have released 98.93% to 99.83% of drug in 7 minutes .

In sublimation method tablet containing (4% Crospovidone) disintegration is faster when compared to others. This can be attributed to the extent water uptake and consequently the strong swelling power of this disintegrant causing sufficient hydrodynamic pressure to induce complete disintegration. The results also showed the decrease in disintegration time as the concentration of superdisintegrants was increased. This can be correlated to tablet matrix pore size distribution created by the use of superdisintegrants, higher the level of disintegrant probably made larger pores with continues network of skeleton providing enough pressure within a matrix for faster disintegration. Formulation with higher concentration of super disintegrant showed increase dissolution rate rapid disintegration with super disintegrant might be one of the probably cause for their faster dissolution and another reason could be that in the presence of superdisintegrant the matrix might have distorted resulting higher surface area, allowing the superdisintegrant to readily pick up water and there by rendering rapid rate of dissolution.

Among the various tablets prepared by the direct compression method containing crospovidone in the concentration of 3% (DCP2) released 99.50% drug with in 8min. were as the tablets prepared by sublimation method with similar concentration of crospovidone (4% SBP3) released 99.83 with in 5 min.

Infrared spectroscopy (IR):

To more different methods are adopted to get the formulated product the excipients used are indomethacin and sodium starch glycolate and second method adopted in the second formulation are subjecting indomethacin and sodium starch glycolate. In this case sodium starch glyconate is a salt are metal salt which has not shown the strong carbonyl carboxylic acid absorption peaks. It is characteristic properties of metal salt of functional group under study. This sodium starch glycolate and indomethacin are mix through by physical mixture. The product obtain exhibited in its IR spectra all the characteristic absorption peaks of drug and polymer suggesting that during this formulation process also they are not under gone any chemical reaction instead of sodium starch glycolate molecule crospovidone is used in this process of formulation. The product obtain in this case also suggest that formulation is a mixture of drug indomethacin and crospovidone when above method are failed to produce any changes in the formulation next step drug and the excipients sodium starch glycolate which subjected for sublimation process the sublimated formulation product also indicate no change in its IR spectrum suggested that characteristic absorption peak of drugand polymer have remain in take.

Same observation is made in the sublimation technique when crospovidone is used in a place of sodium starch glycolate suggesting that during this method of preparation drug under investigation remade in an unreacted form and available for any biochemical applications.

SUMMAY AND CONCLUSION:

The data obtain from the study of Formulation and evaluation of mouth dissolving tablet containing Indomethacin solid dispersion prepared by different method using carriers like PVP-K30, PEG-4000, PEG-6000 and Sodium starch glycolate, Crospovidone the following points can be conclude

- The Indomethacin Solid dispersion were prepared by solvent evaporation method and physical mixture using PVP-K30 and PEG-4000, PEG-6000 (in weight ratios).
- The solubility of Indomethacin was enhanced in presence of carriers (PVP- K30, PEG-4000 and PEG-6000)
- The dissolution rate of Indomethacin from solid dispersion i.e., F3 and F24 was significantly higher than that of pure drug.
- Solid dispersion prepared by Solvent evaporation method showed faster drug release than the solid dispersion prepared by physical mixture.
- The general trend indicated that there was increase in dissolution rate for solid dispersion in the following order of PVP-K30 > PEG - 6000 > PEG – 4000.
- IR studies indicated that no chemical interaction between drug and polymer took place during preparation of solid dispersion of Indomethacin.
- DSC studies indicated that Indomethacin was homogeneously distributed within the carrier in an amorphous state and no drug crystallized out of the dispersion suggesting that drug and polymer exist in the form of a mixture rather than the reaction product.
- Solid dispersion system with PEG 4000, and PEG600 by solvent evaporation method, the crystallinity of indomethacin was found to be reduced to a greater extent, evidenced by marked reduction in the number as well as the intensity of peaks. The XRD pattern of solid dispersion systems prepared with PVP-K30 by solvent evaporation method shows complete disappearance of intense peaks suggested amorphization of indomethacin.
- Tablet prepared by direct compression and sublimation methods were found to be good and were free from chipping and capping.
- The low values of the standard deviation of average weight of the prepared tablets indicate weight uniformity within the batches prepared.
- The hardness of the prepared tablets was found to be in the range 2.4 kg/cm2 to 3.2 kg/cm2.The friability values of the prepared tablet were found to be less than 1%.
- IR spectroscopic studies indicated that the drug is compatible with all the excipients.
- The in vitro disintigration time of indomethacin prepared by direct compression and sublimation method were found to be in the range of 21 to 53 sec fulfilling the official requirements.
- The wetting time of indomethacin prepared by direct compression and sublimation method were found to be in the range of 12 to 41 sec.
- The drug content of tablets was uniform in all the batches and was between 98.16 to 99.72%.
- The drug release from mouth dissolving tablets of indomethacin prepared by direct compression and sublimation methods were found to be in the range of 98.75 to 99.93% and the result of DCP2 showed 99.83% drug release with in 8 min and SBP3 showed 99.93% drug release within 5 minute.
- The stability study shows that no significant changes in tablets hardness, friability, disintegration time and in vitro dissolution time after one month study.
- Among the two methods used namely direct compression and sublimation, the sublimation method was found to be superior to direct compression method for the preparation of mouth dissolving tablet of Indomethacin.

REFERENCES:

1. Aurora J. and Pathak V. Oral Disintegrating Technologies: Oral Disintegrating Dosage Forms: An Overview, Drug Deliv. Technol. 2005; 5 (3): 50–54.
2. Bandari S. Orodispersible tablets An Overview, Asian J. Pharm.2008; 1: 2-11.
3. Panigrahi D, Baghel S, and Mishra B. Mouth dissolving tablets:an overview of preparation techniques, evaluation and patentedtechnologies. J. Pharm. Res. 2004; 4(3):33–38.
4. Ghosh T.K. "Orally Disintegrating Tablets," AAPSNewsmagazine, 2004, 7 (6), 19-21.
5. Pather S.I., Khankari R., and Siebert J,"Quick-DissolvingIntraoral Tablets," in Drug Delivery to the Oral Cavity:Molecules to Market Ghosh T.K. and Pfister W.R., Eds. (CRCPress, New York, NY, 2005), pp. 291–336.
6. Stetsko G. Statistical experimental design and its application to pharmaceutical development problems. Drug Dev Ind. Pharm. 1986; 12:1109-1123.
7. Gohel M, Formulation design and optimization of mouth dissolve tablets of nimesulide using vacuum drying technique. AAPS PharmSciTech. 2004; 5:E36.
8. Omaima A. Sammour, Formulation and Optimization of Mouth Dissolve Tablets

Containing Rofecoxib Solid Dispersion. AAPS PharmSciTech 2006; 7 (2) Article 55 .
9. Zaghloul A, Faltinek J, Reddy IK, Khan MA. Response surface methodology to obtain naproxen controlled release tablets from its microspheres with Eudragit L 100-55. J Micro-encapsul. 2001; 18(5):651-662.
10. Lucas S: The Pharmacology of Indomethacin. Headache. 2016 Feb;56(2):436-46. doi: 10.1111/head.12769. Epub 2016 Feb 11. [Article]
11. Helleberg L: Clinical Pharmacokinetics of indomethacin. Clin Pharmacokinet. 1981 Jul-Aug;6(4):245-58. doi: 10.2165/00003088-198106040-00001. [Article]
12. Nalamachu S, Wortmann R: Role of indomethacin in acute pain and inflammation management: a review of the literature. Postgrad Med. 2014 Jul;126(4):92-7. doi: 10.3810/pgm.2014.07.2787. [Article]
13. Pacifici GM: Clinical pharmacology of indomethacin in preterm infants: implications in patent ductus arteriosus closure. Paediatr Drugs. 2013 Oct;15(5):363-76. doi: 10.1007/s40272-013-0031-7. [Article]