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FORMULATION AND OPTIMIZATION OF MOUTH DISSOLVING TABLETS CONTAINING INDOMETHACIN SOLID DISPERSION

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Abstract:
Oral drug delivery is the most widely used route of drug administration among all the routes that have been explored for the systemic delivery via various pharmaceutical products of different dosage forms. Aim of the present work is to formulate the indomethacin tablets to present it in the form of. To develop and over an extended period of time in the gastro intestinal track and compared the in-vitro dissolution profile with that of the marketed product. It was deduced that MDTs of Indomethacin formulated by direct compression method. The superdisintegrants were used in formulation to ameliorate the disintegration of tablets. It produces better patient compliance and effective therapy of tablets. Also, the bitter drug can be easily formulated as mouth dissolving tablets by masking their taste using aspartame as taste masking agent. It was also found that the superdisintegrants are effective at an optimum concentration, on increasing the ratio of Crospovidone and Sodium starch glycolate concentration above their optimum concentration this enhance the gelling effects of formulation. The formulation TC7 exhibited better results as compared to other formulations. Further these formulations can be select for in vivo study.
Key words: Formulation, Optimization, Mouth Dissolving Tablets, Indomethacin, Solid Dispersion

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INTRODUCTION:

Oral drug delivery is the most widely used route of drug administration among all the routes that have been explored for the systemic delivery via various pharmaceutical products of different dosage forms (Ghosh et al., 2005) because of its distinct advantages of ease of administration, improved patient compliance, flexibility in designing the dosage form, least sterility requirements and avoidance of pain compared to parenteral route (Krishnaiah et al., 2002, Saurabh et al., 2011, Prabhu et al., 2011, Bhalla et al., 2012). Tablets and capsules are the most popular solid dosage forms administered orally. It is estimated that 50 % of the population is affected by dysphasia (difficulty in swallowing), which is the major limitation associated with solid dosage forms such as tablet (Barnhart et al., 2007). In addition, it may pose problem for pediatric and geriatric patients who find swallowing difficult and for the treatment of some patients when water is not available in the case of motion sickness (kinetosis) and sudden attack of coughing during the common cold and bronchitis (Gryczke et al., 2011, Tritthart et al., 2001). This can be resolved by the preparation of rapidly dispersing or dissolving oral forms that combines both the properties of liquid and tablet dosage forms (Habibh et al., 2000).

The orally disintegrating tablets are also called as orodispersible tablets (ODTs), quick disintegrating tablets, fast disintegrating tablets, fast dissolving tablets. United States Food and Drug Administration (US FDA) defined ODTs as “a solid dosage form containing medicinal substances or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue”. US FDA further defines ODTs as solid oral preparations that disintegrate rapidly in the oral cavity with an in-vitro disintegration time of approximately 30 s or less (Guidance for industry, 2008). In addition, ODTs should have an acceptable taste and very short disintegration time, generally from few seconds to about a minute, in the mouth. It is always a challenge to prepare ODTs having short oral disintegration time as it is with positive correlation with the mechanical strength of the tablets (Szakonyi et al., 2013). Indomethacin belongs to non-steroidal anti-inflammatory drug class, which is used to reduce fever, pain and inflammation associated with musculo-skeletal and joint disorders including ankylosing spondolysis, rheumatoid arthritis, osteoarthitis and acute gout (Shen, 1982, Kulmacz, 1989, Nunchanit et al., 2013). It is described as Class II (poorly aqueous solubility and high permeability) drug in BCS. So, it is proposed to develop ODT dosage form of indomethacin to increase its solubility and subsequently bioavailability.

Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) commonly used for the reduction of pain and inflammation caused by condition such as osteoarthritis, gout, ulcerative colitis, colon cancer. Its biological half-life is 4.5 hrs.

When given conventionally it gets released in the upper GIT thereby causing irritation and ulcer in the upper GIT. The dosage form should be designed in such a way that it should minimize or prevent drug release in the acidic environment of upper GIT and start releasing the drug in a controlled manner once it reaches the alkaline environment of small intestine.

Aim of the present work is to formulate the indomethacin tablets to present. To develop and over an extended period of time in the gastro intestinal track and compared the in-vitro dissolution profile with that of the marketed product.

MATERIALS AND METHODOLOGY:

MATERIALS

Indomethacin Procured from**,** Provided by Chandra labs Hyderabad. Ethyl cellulose, Sodium lauryl sulfate, Hydroxy propyl cellulose, Povidone-K30 are Standard chemical Reagents

METHODOLOGY

Preformulation studies of pure drug

Determination of λ_{max}

The purity of drug paly important role in formulation of dosage forms. The efficacy of any drug depends on the purity of drugs. There are number of methods can be applied to determine the purity of drugs. Among all the methods the UV spectroscopy is best because it is cheap and produces reliable and reproducible results. In UV spectroscopy the λ_{max} of the drug can be determined. The λ_{max} of drug are specific and it cannot be change at specific conditions. When λ_{max} of compound will change then it indicates that compounds have lost its actual purity.

In our study we determined the λ_{max} of Indomethacin by using UV spectroscopy. The solution of Indomethacin containing concentration of 10µg/ml was prepared in water, and UV spectrum was taken using UV spectrophotometer. The sample was scanned in the range of 200-400 cm^{-1}

Preparation of calibration curve in pH 6.8 phosphate buffer

An accurately weighed amount of Indomethacin corresponding to 100mg was dissolved in a small

amount of pH 6.8 Phosphate Buffer in 100ml volumetric flask and volume made up to 100ml with the same pH 6.8 Phosphate Buffer. From this stock's solution, 1ml, 2ml, 3ml, 4ml, 5ml, 6ml, 7ml, 8ml, 9ml and 10ml were withdrawn and diluted up to 10ml with the Ph 6.8 Phosphate Buffer in 10ml volumetric flask to get concentration of 1µg, 2µg, 3µg, 4µg, 5µg, 6µg, 7µg, 8µg, 9µg and 10µg respectively. The optical density of every solution was calculated by UV-Visible Spectrophotometer at 260 nm for Indomethacin using pH 6.8 Phosphate Buffer as blank.

Preparation of calibration curve in 0.1 N NaOH

An accurately weighed amount of Indomethacin 100mg was dissolved in small amount of 0.1 N NaOH in 100ml volumetric flask and volume made up to 100ml with the same 0.1 N NaOH. From this stock's solution, 1ml, 2ml, 3ml, 4ml, 5ml, 6ml, 7ml, 8ml, 9ml and 10ml were withdrawn and diluted up to 10ml with the 0.1 N NaOH in 10ml volumetric flask to get concentration of 1µg, 2µg, 3µg, 4µg, 5µg, 6µg, 7µg, 8µg, 9µg and 10µg respectively. The optical density of every solution was calculated by UV- Visible Spectrophotometer at 260 nm for Indomethacin 0.1 N NaOH as blank.

Drug excipients interaction study by FTIR

The Fourier Transform – Infrared (FT-IR) spectroscopy has numerous applications in pharmaceutical field. It is widely used in determination of identification of known and unknown compound. Apart from this it can also be used in evaluating the drug interaction. During formulation the active ingredient are used mixed with various excipients to give proper shape and appearance. Sometimes it happens after mixing the active ingredients with excipient, it produces incompatibility due to drug excipient interaction. The incompatibility of drug can alter the potency of formulation. It can also produce adverse effects to the body. Hence for pharmaceutical industries it is prime work to check the drug and excipient incompatibility.

Solubility analysis

The preparation of any dosage form, it required to know the solubility of drug. The solid dosage form needs particular solvent to dissolve, and produces pharmacological effect to body. Additionally, the bioavailability of drug present in solid dosage form depends upon solubility of drug. If drug is sparingly soluble in solvent, then it produces minimum therapeutic response due to less availability of drug to receptors. Hence solubility of drug play important role in therapeutic effects of drug.

Determination of melting point

The melting point of drugs indicates the purity of drug. Every drug has its own melting point at particular conditions. If there is any alteration in melting point of drug it inferred the change in therapeutic response of drug. When active constituents are incorporated with foreign particles or adulterants, it changes the melting point of active constituents. When drug comes in contact with moisture then it also changes the melting point of drugs. Hence melting point of drug is best indicator to check the purity of drug. If drug is pure than it will produces maximum or desired therapeutic effect to the body.

Formulation

Tablets of Indomethacin were prepared by direct compression method. All the formulation ingredients mentioned in formulation table 1 and table 2 were weighed accordingly and mixed in a mortar and pestle. This powder blend was then allowed to dry for few moments and then again mixed well and passed through sieve no 60. Then blend was used for further processing.

Table 1: Formulation of mouth dissolving Indomethacin tablets

Ingredients	T1	T2	T3	T4	T5	T6	T7	T8
Indomethacin	150	150	150	150	150	150	150	150
Crospovidone	8	8	8	8	10	10	10	10
Sodium starch glycolate	7	9	11	13	7	9	11	13
Microcrystalline cellulose	20	20	20	20	20	20	20	20
Mannitol	114	112	110	108	112	110	108	106
Mg. Stearate	3	3	3	3	3	3	3	3
Talc	1	1	1	1	1	1	1	1
Aspartame	2	2	2	2	2	2	2	2
Theoretical Weight	305	305	305	305	305	305	305	305

RESULTS AND DISCUSSION:

Identification of drug

Identification of drug by UV spectroscopy

The Indomethacin were identified by UV spectroscopy method. The Indomethacin exhibited maximum absorption at 260 nm. These wavelengths were considered as λ_{max} for samples and all the observations by UV spectrophotometer to calculate the amount of drug were taken at this wavelength.

Standard curves of Indomethacin

The standard curves of Indomethacin were prepared in phosphate buffer pH 6.8 and 0.1 N NaOH; and results depicted in table 2

The calibration curve was drawn for Indomethacin in pH 6.8 phosphate buffer, and it shows straight line in range of concentration from 1 to 10 µg/ml with R^2 value of 0.9937 which follows Beer-Lambert law (Fig 1). Calibration curve of Indomethacin in 0.1 N NaOH shows straight line in range of 1 to 10 µg/ml with R^2 value of 0.9953 which follows Beer-Lambert law (Fig 2). The outcomes inferred that Indomethacin produces higher R^2 value in pH 6.8 phosphate buffer; it indicates better solubility in phosphate buffer solution.

Indomethacin showed good linearity in all the solution systems at a concentration range of 1-10 µg/ml.

Table 2: Absorbance by Indomethacin drug at different concentration in pH 6.8 phosphate buffer

S. No.	Concentration in µg/ml	Absorbance at 260 nm
1.	1	0.023
2.	2	0.042
3.	3	0.073
4.	4	0.098
5.	5	0.121
6.	6	0.140
7.	7	0.158
8.	8	0.176
9.	9	0.212
10.	10	0.242

Figure 1: Calibration curve of Indomethacin drug in pH 6.8 phosphate buffer

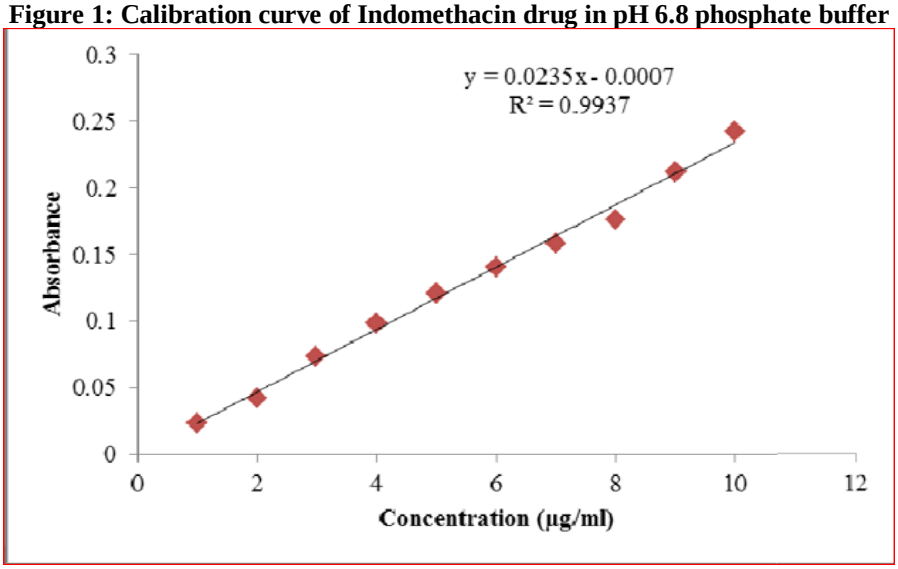

Table 3: Absorbance by Indomethacin drug at different concentration in N NaOH

S. No.	Concentration in µg/ml	Absorbance at 260 nm
1.	1	0.019
2.	2	0.056
3.	3	0.069
4.	4	0.091
5.	5	0.118
6.	6	0.133
7.	7	0.159
8.	8	0.184
9.	9	0.207
10.	10	0.238

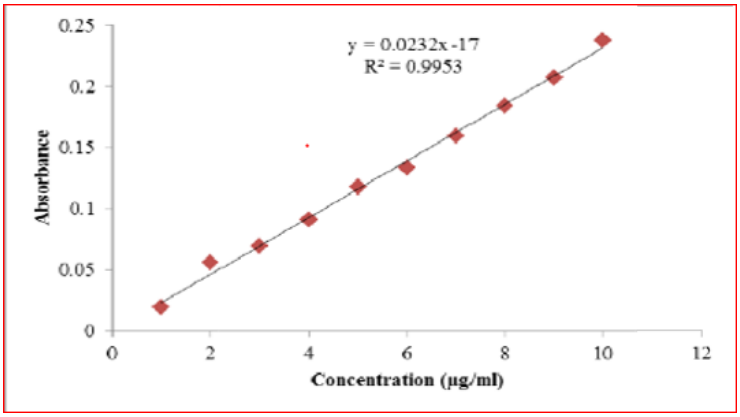

Figure 2: Calibration curve of Indomethacin drug in 0.1 N NaOH

Drug polymer compatibility studies

The major IR (v cm^{-1}) spectrum of Indomethacin showed absorption bands at 3424.49 (O-H, free hydroxyl group), 2928.72 (Cyclic C-H, str), 2861.31 (Ali- C-H, str), 1731.19 (C=O stretch), 1455.75 (C-C ring stretch), 1252.19 to 1135.86 (C-C stretching), 1061.24 (-CO, stretch), 809.14 (O-H, out of plane bend), 625.05 (Out of plane C=C) (Fig 3).

The major IR (v cm^{-1}) spectrum of Indomethacin and excipient showed absorption bands at 3444.75 (O-H, free hydroxyl group), 2928.40 (Cyclic C- H, str), 2860.84 (Ali- C-H, str), 1732.45 (C=O stretch), 1455.37 (C-C ring stretch), 1250.05 to 1135.24 (C-C stretching), 1060.14 (-CO, stretch), 807.81 (O-H, out of plane bend), 626.20 (Out of plane C=C) (Fig 4).

The IR peaks of Indomethacin and mixture (Indomethacin and excipient) exhibits no major deviation, it indicates that there was interaction between drug and excipients.

After performing FTIR of the best formulation of Indomethacin mouth dissolving tablet it was found that the peaks obtained were in between the range of main principal peaks and were found to be very near to previously performed FTIR of pure drug Indomethacin. No major deviation in peaks were obtained in IR spectra, hence this indicates that drug was compatible with other tablet ingredients (Fig 3 to Fig 4).

The results of IR spectra suggest that selection of excipient for mouth dissolving tablets were suitable. Hence it cannot alter the therapeutics efficacy of Indomethacin and it also support to continue further research works.

From the outcomes of UV spectroscopy and IR, we confirmed that the Indomethacin was pure and it free from incompatibly with excipient. Consequently, we planned to conduct further research work.

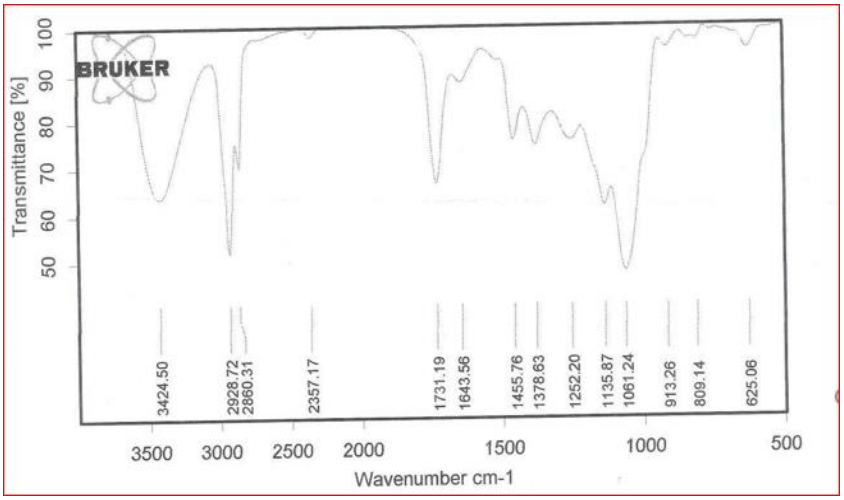

Figure 3:FTIR spectra of Indomethacin

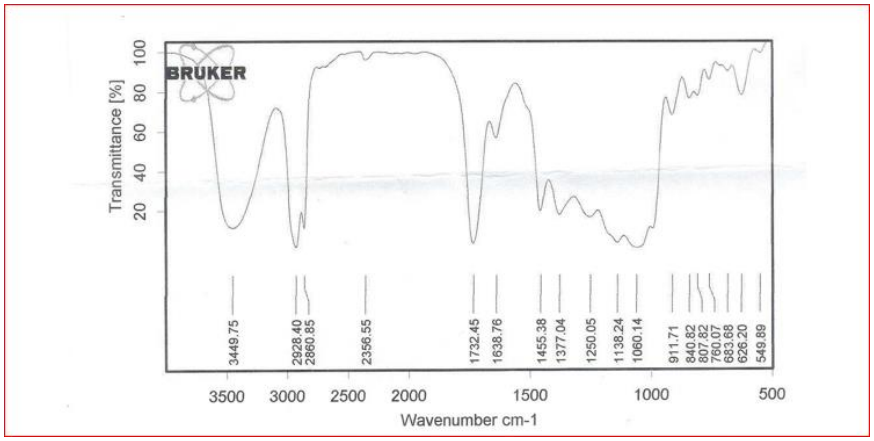

Figure 4: FTIR spectra of Indomethacin – excipient mixture

Solubility analysis

The pure drug sample of Indomethacin was found to be freely soluble in water, methanol and chloroform, while sparingly soluble in acetone and insoluble in benzene.

Determination of melting point

Melting point of pure Indomethacin was found to be 175-178 ˚C was in range of 176˚- 178 ˚C, actual melting point of Indomethacin as per pharmacopoeia. The results of melting points of Indomethacin were in the range of reported melting point of Indomethacin by pharmacopoeia. It also inferred the purity of drugs.

Characterization of mouth dissolving tablets

Assessment of pre-compression characteristics of powder blend

The Pre-compression evaluations of prepared powders were shown below. The powders were estimated for bulk density, tapped density, Hausner's ratio and angle of repose and consistency in data obtained as indicated by their standard deviation values.

Pre-compression characteristics were investigated for all 8 formulations of both drugs and the study showed following results.

Evaluation of pre-compression characteristics of Indomethacin powder blend

Bulk density and tapped density of different formulations were calculated. The result of bulk density ranges from 0.473 to 0.574 and tapped density from 0.565 to 0.698. Hausner's ratio was found to be in between 1.14 to 1.23; and Compresibility Index from 12.74 to 19.34. Angle of repose exhibited good to excellent flow properties of the powdered blend (Table 4).

The pre-compression study of Indomethacin indicates that mouth dissolving tablets can be prepared by direct compression methods.

Table 4: Data of pre-compression characteristics of Indomethacin powder blend

Parameters	T1	T2	T3	T4	T5	T6	T7	T8
Mean Angle of repose* ± S.D.	36° 25' ± 0.02	29° 36' ± 0.11	31° 28' ± 0.05	30° 57' ±0.08	29° 91' ± 0.09	31° 43' ± 0.13	34° 72' ± 0.21	38° 14' ± 0.05
Mean Apparent bulk density* (g/cm^3) ± S.D	0.473 ± 0.02	0.565 ± 0.04	0.547 ± 0.06	0.513 ± 0.01	0.574 ± 0.03	0.519 ±0.06	0.538 ±0.04	0.558 ±0.04
Mean Tapped bulk density* (g/cm^3) ± S.D.	0.565 ± 0.03	0.689 ± 0.01	0.672 ± 0.03	0.621 ± 0.06	0.698 ± 0.04	0.625 ± 0.03	0.645 ±0.02	0.672 ±0.02
Compresibility Index* (%)	12.74	15.09	17.11	17.39	14.89	15.36	16.59	19.34
Hausner's Ratio*	1.14 ± 0.01	1.17 ± 0.02	1.20 ± 0.04	1.21 ± 0.02	1.17 ± 0.05	1.18 ± 0.02	1.20 ± 0.05	1.23 ± 0.03

*Value shown in tables is mean of three determinations

Evaluation of mouth dissolving tablet of Indomethacin

The physicochemical character of mouth dissolving tablet of Indomethacin was evaluated, and results in below table. The tablet dimension includes diameter and thickness of tablets. Thickness of all formulations was found to be between 3.21 to 3.62.

it has been observed that tablet weights of all formulation were under USP limits, between 305 ± 1 mg. The tablets of all batches exhibited the hardness between 3.05 to 3.73 (Kg/cm^2) which is acceptable limits, which shows in the literature. The result of friability, inferred that all formulation can have ability to withstand shocks, because the percentage friability was less than 1%. The data of uniformity of content which was performed by UV spectroscopy and all the formulation exhibited drug content between 97.61 to 99.25 %.

In direction of the industrial scientists, various indications of tablet like flow property, dimension hardness, drug content etc. were calculated which outcomes in successful trials.

The wetting time and water absorption ratio were noted 17.79 to 35.07 seconds and 39.24 to 73.38 seconds respectively. The wetting time of Indomethacin mouth dissolving tablets was enhanced on increasing the concentration of Crospovidone and Sodium starch glycolate. The water absorption of Etoperidone mouth dissolving

tablets was decreased on enhancing the concentration of Crospovidone and Sodium starch glycolate.

The disintegration time of mouth dissolving tablets ranges from 38.21 to 22.36 seconds. The disintegration time of Indomethacin mouth dissolving tablets was decreased on enhancing the concentration of Crospovidone and Sodium starch glycolate.

From above result it has been observed that T7 formulation exhibited excellent wetting time, water absorption ratio and disintegration time as compared to other formulations. Moreover, the T8 formulation exhibited lowest wetting time and disintegration time; and highest water absorption ratio. This parameter increases due to gelling and its consequent viscosity producing effects.

The post compression findings of Indomethacin mouth dissolving tablets inferred that composition used in the formulation of tablets were satisfactorily.

Table 5: Evaluation of Indomethacin mouth dissolving tablets

Parameters	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**
Uniformity of weight (mg)*	305.20 ± 1.12	304.17 ± 1.07	304.84 ± 2.01	305.07 ± 1.81	304.6 ± 1.92	305.51 ± 1.25	304.30 ± 1.58	305.42 ± 1.34
Thickness (mm)*	3.21 ± 0.01	3.50 ± 0.04	3.10 ± 0.03	3.34 ± 0.02	3.17 ± 0.01	3.27 ± 0.05	3.41 ± 0.03	3.62 ± 0.04
Friability (%)*	0.28 ± 0.02	0.19 ± 0.01	0.24 ± 0.03	0.27 ± 0.01	0.29 ± 0.05	0.22 ± 0.06	0.20 ± 0.02	0.25 ± 0.01
Tablet Hardness (Kp)*	3.29 ± 0.06	3.18 ± 0.03	3.51 ± 0.06	3.05 ± 0.04	3.62 ± 0.07	3.21 ± 0.05	3.73 ± 0.03	3.42 ± 0.04
Assay (%)	98.37 ± 0.15	99.25 ± 0.72	98.74 ± 0.12	99.18 ± 0.34	97.61 ± 0.53	98.24 ± 0.79	99.15 ± 0.47	98.05 ± 0.25

*Average of three times measure

Table 6: Evaluation of wetting time of Indomethacin mouth dissolving tablets

Formulation	Wetting time (Sec)
T1	35.07±0.02
T2	30.52±0.05
T3	28.36±0.12
T4	25.73±0.19
T5	28.46±0.08
T6	23.91±0.17
T7	21.32±0.09
T8	17.79±0.13

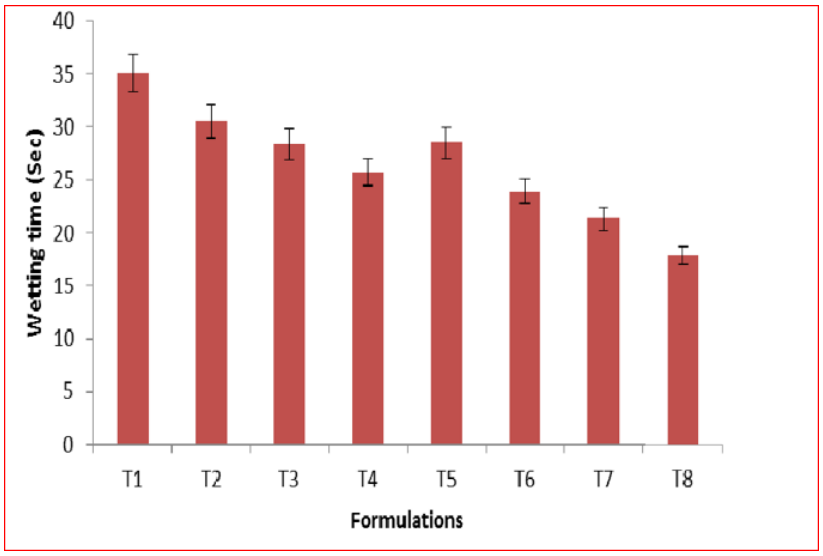

Figure 5: Wetting time of Indomethacin mouth dissolving tablets

Table 7: Evaluation of Water absorption ratio of Indomethacin mouth dissolving tablets

Formulation	Water absorption ratio
T1	39.24±1.01
T2	46.83±1.24
T3	52.64±0.78
T4	64.71±1.37
T5	50.57±1.29
T6	61.27±0.97
T7	68.19±1.07
T8	73.38±1.15

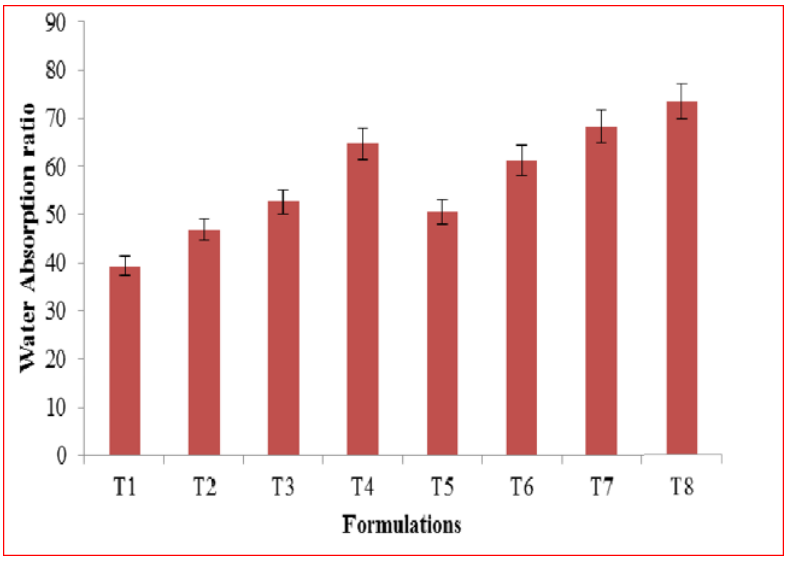

Figure 6: Water absorption ratio of Indomethacin mouth dissolving tablets

Table 8: Evaluation of in-vitro disintegration time of Indomethacin mouth dissolving tablets

Formulation	In-vitro disintegration time (sec)
T1	38.21±0.08
T2	35.18±0.12
T3	34.52±0.07
T4	29.73±0.08
T5	31.61±0.19
T6	28.45±0.09
T7	27.58±0.10
T8	22.36±0.05

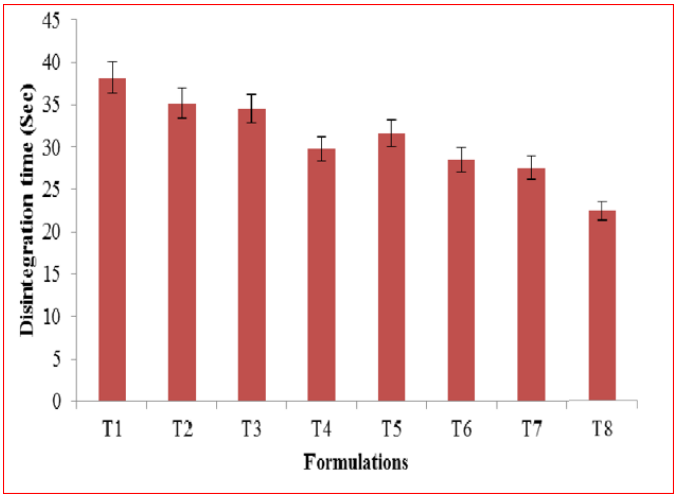

Figure 7: Disintegration time of Indomethacin mouth dissolving tablets

In vitro drug release studies

Indomethacin mouth dissolving tablets

In-vitro dissolution studies revealed that 78 to 100% of drug release from various formulations. The 50% of the drug was released from the formulations T7 and T8 within 4 minutes. The T1 released minimum drug among all other formulations i.e., 78.23% on 14th minutes. The T2 released 86.42% drug at 14th minutes. The T3 released 88.19% drug at 14th minutes. The T4 released 91.53% drug at 14th minutes. The T5 released 90.73% drug at 14th minutes. The T6 released 93.67% drug at 14th minutes. The T7 released 98.16% drug at 14th minutes. The T8 released 95.62% drug at 12th minutes. The T8 released maximum drugs at 12th minutes. From above finding it has been noticed that on increasing the concentration of Crospovidone it decreased the drug release from tablets.

The rapid drug dissolution might be due to easy breakdown of particle by superdisintegrant action. From in vitro dissolution data, it was observed that 98.16% of Indomethacin released in 14 minutes indicates that the tablet complies as per IP specifications, that is, 85%–110%. Tables represents the log cumulative percent drug release and log cumulative percent drug remain in Indomethacin mouth dissolving tablets respectively. The dissolution rate was found to increase linearly with increase in the concentration of superdisintegrant. Mechanism it followed was wicking and swelling with minimum gelling. It was observed that T8 formulation released 65.62% drug in 12 minutes. This formulation has large amount of superdisintegrant that may cause tablets fragile. So that T7 was selected for further studies.

Table 9: In-vitro dissolution study of Indomethacin mouth dissolving tablets

Time in mins	Sq.rt. of Time	Log Time	Cumulative percent drug release							
			T1	T2	T3	T4	T5	T6	T7	T8
0	0	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	1.41	0.30	23.54	24.15	26.32	27.42	26.14	27.52	29.43	32.35
4	2	0.60	38.26	40.32	43.54	44.73	45.36	48.17	51.72	68.48
8	2.82	0.90	54.72	58.14	65.75	69.34	62.43	69.31	73.64	84.51
12	3.46	1.07	69.61	75.37	76.47	79.49	79.18	82.82	86.29	95.62
14	3.74	1.14	78.23	86.42	88.19	91.53	90.73	93.67	98.16	-

Table 10: Log cumulative percent drug release from Indomethacin mouth dissolving tablets

Time in mins	Sq.rt of Time	Log Time	Log cumulative percent drug release							
			T1	T2	T3	T4	T5	T6	T7	T8
0	0	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	1.41	0.30	1.37	1.38	1.42	1.43	1.41	1.43	1.46	1.50
4	2	0.60	1.58	1.60	1.63	1.65	1.65	1.68	1.71	1.83
8	2.82	0.90	1.73	1.76	1.81	1.84	1.79	1.84	1.86	1.92
12	3.46	1.07	1.84	1.87	1.88	1.90	1.89	1.91	1.93	1.98
14	3.74	1.14	1.89	1.93	1.94	1.96	1.95	1.97	1.99	-

Table 11: Log cumulative percent drug remain in Indomethacin mouth dissolving tablets

Time in mins	Sq. rt. of Time	Log Time	Log cumulative percent drug remain							
			T1	T2	T3	T4	T5	T6	T7	T8
0	0	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	1.41	0.30	1.88	1.87	1.86	1.86	1.86	1.86	1.84	1.83
4	2	0.60	1.79	1.77	1.75	1.74	1.73	1.71	1.68	1.49
8	2.82	0.90	1.65	1.62	1.53	1.48	1.57	1.48	1.42	1.19
12	3.46	1.07	1.48	1.39	1.37	1.31	1.31	1.23	1.13	0.64
14	3.74	1.14	1.33	1.13	1.07	0.92	0.96	0.80	0.26	-

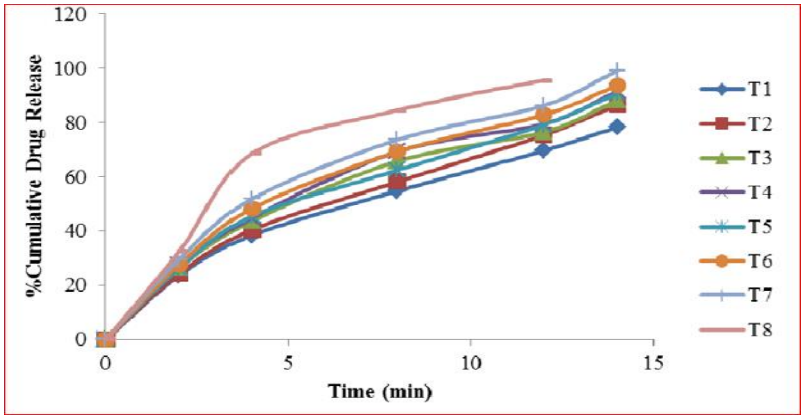

Figure 8: In-vitro drug release profile of Indomethacin mouth tablets according to zero order release

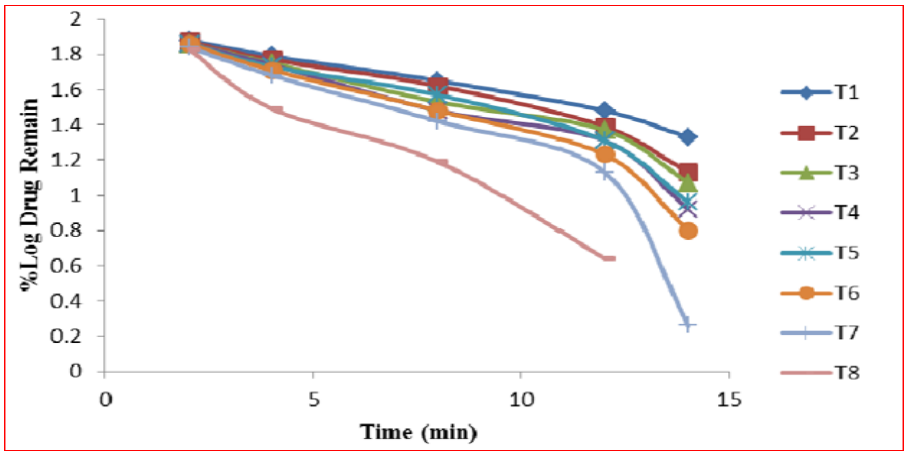

Figure 9: In-vitro drug release profile of Indomethacin mouth tablets according to first order release

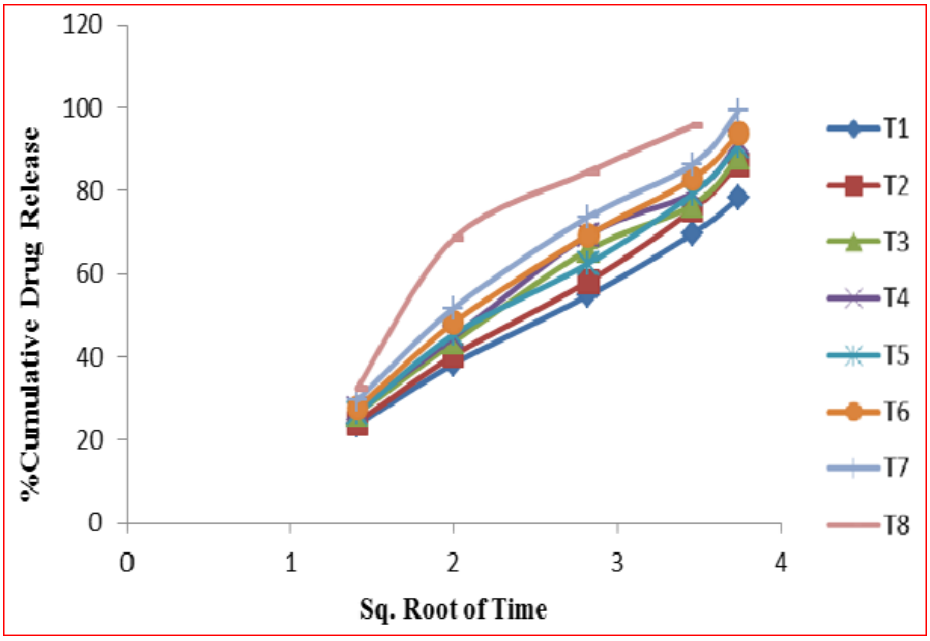

Figure 10: In-vitro drug release profile of Indomethacin mouth dissolving tabletsaccording to higuchi's model

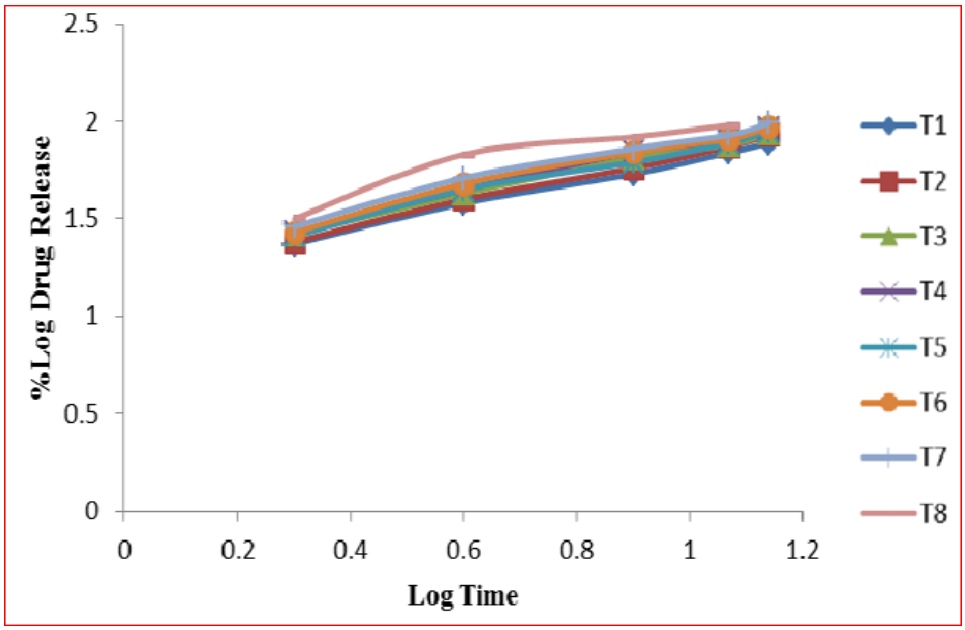

Figure 11: In-vitro drug release profile of Indomethacin mouth dissolving tablets

Kinetics of in vitro drug release of Indomethacin mouth dissolving tablets

The formulations of Indomethacin tablets were subjected to four model fitting analysis namely, zero order (Fig 8), first order (Fig 9), Higuchi (Fig 10) and Korsmeyer-peppas model (Fig 11). That all the formulations follow the higuchi order kinetics as the co-efficient of regression (R^2) was nearer to unity as compared to the regression value of zero order and first order model. Among all the formulations it was observed that R^2 value of formulation T7 was nearer to one than formulations. On the basis of this parameter, T7 was selected for further study.

Table 12: Kinetics of in vitro drug release profile of Indomethacin mouth dissolving tablets

nulation code	Zero order	First order	Higuchi	Korsmeyer and Peppas Model	
	R^2	R^2	R^2	n	R^2
T1	0.929	0.999	0.997	0.603	0.996
T2	0.943	0.989	0.994	0.634	0.996
T3	0.916	0.990	0.991	0.603	0.994
T4	0.914	0.983	0.990	0.615	0.991
T5	0.929	0.980	0.992	0.614	0.989
T6	0.912	0.982	0.993	0.615	0.984
T7	0.908	0.918	0.998	0.601	0.982
T8	0.849	0.982	0.907	0.599	0.902

Model fitting analysis of formulations of Indomethacin

The values of n in Korsmeyer- peppas model suggested that all formulations of Indomethacin tablets follow Non Fickian Anamolous.

Table 13: Model fitting analysis of all the formulation of Indomethacin

Formulation code	Value of n	R^2 Value	Mode of transport
T1	0.603	0.996	Non Fickian Anamolous
T2	0.634	0.996	Non Fickian Anamolous
T3	0.603	0.994	Non Fickian Anamolous
T4	0.615	0.991	Non Fickian Anamolous
T5	0.614	0.989	Non Fickian Anamolous
T6	0.615	0.984	Non Fickian Anamolous
T7	0.601	0.982	Non Fickian Anamolous
T8	0.599	0.902	Non Fickian Anamolous

Factorial design

The amounts of the superdisintegrants (Crospovidone, X_1 and Sodium starch glycolate, X_2) were chosen as independent variables in a 3^2 full factorial design

Table 14: Formulation of full factorial design of Indomethacin mouth dissolving tablets

Ingredients	TC1	TC2	TC3	TC4	TC5	TC6	TC7	TC8	TC9
Tolperisone	150	150	150	150	150	150	150	150	150
X_1	-1	-1	-1	0	0	0	+1	+1	+1
X_2	-1	0	+1	-1	0	+1	-1	0	+1
Microcrystalline cellulose	20	20	20	20	20	20	20	20	20
Mannitol	109	108	108	108	108	107	108	107	107
Mg. Stearate	3	3	3	3	3	3	3	3	3
Talc	1	1	1	1	1	1	1	1	1
Aspartame	2	2	2	2	2	2	2	2	2

X_1 - Crospovidone, X_2 - Sodium starch glycolate

Table 15: Formulation layout for factorial batches of Indomethacin

Formulation	Coded value		Uncoded value	
	X_1	X_2	X_1	X_2
TC1	-1	-1	9.5	10.5
TC2	-1	0	9.5	11.0
TC3	-1	+1	9.5	11.5
TC4	0	-1	10.0	10.5
TC5	0	0	10.0	11.0
TC6	0	+1	10.0	11.5
TC7	+1	-1	10.5	10.5
TC8	+1	0	10.5	11.0
TC9	+1	+1	10.5	11.5

Evaluation of factorial Design mouth dissolving tablet of Indomethacin

The results of friability, assay, wetting time, water absorption ratio, in-vitro disintegration time and dissolution study of factorial design mouth dissolving tablets of Indomethacin,

Evaluation of factorial Design mouth dissolving tablet of Indomethacin

Friability of all the formulation displayed % friability less than 1% that reveals the ability of tablets to withstand shocks, which may encounter. The data of uniformity of content which was performed by UV spectroscopy displayed that tablets of all batches had drug content within USP limits i.e. between 98.32 to 99.89%).

The wetting time and water absorption ratio were found to be 17.02 to 20.57 seconds and 68.87 to 75.31 seconds, respectively. The disintegration time of factorial design mouth dissolving tablets ranges from 21.79 to 25.34 seconds .

From above result it has been observed that TC7 formulation exhibited excellent wetting time, water absorption ration and disintegration time as compared to other formulations. Moreover, the TC8 formulation exhibited lowest wetting time and disintegration time; and highest water absorption ratio. This parameter enhances due to gelling and its subsequent viscosity producing effects.

Table 16: Evaluation of factorial design Indomethacin mouth dissolving tablets

Parameters	TC1	TC2	TC3	TC4	TC5	TC6	TC7	TC8	TC9
Friability (%)*	0.21 ± 0.03	0.18 ± 0.04	0.22 ± 0.02	0.23 ± 0.05	0.21 ± 0.03	0.20 ± 0.07	0.21 ± 0.04	0.19 ± 0.08	0.20 ± 0.05
Assay (%)	98.56 ± 0.84	98.61 ± 0.75	99.28 ± 0.39	98.43 ± 0.54	98.32 ± 0.72	99.47 ± 0.67	99.89 ± 0.28	97.26 ± 0.42	99.67 ± 0.91

*Average of three times measure

Table 17: Evaluation of wetting time of factorial design Indomethacin mouth dissolving tablets

Formulation	Wetting time (Sec)
TC1	20.57±0.03
TC2	20.14±0.02
TC3	19.87±0.05
TC4	19.69±0.03
TC5	18.92±0.02
TC6	18.23±0.05
TC7	17.78±0.07
TC8	17.50±0.09
TC9	17.02±0.08

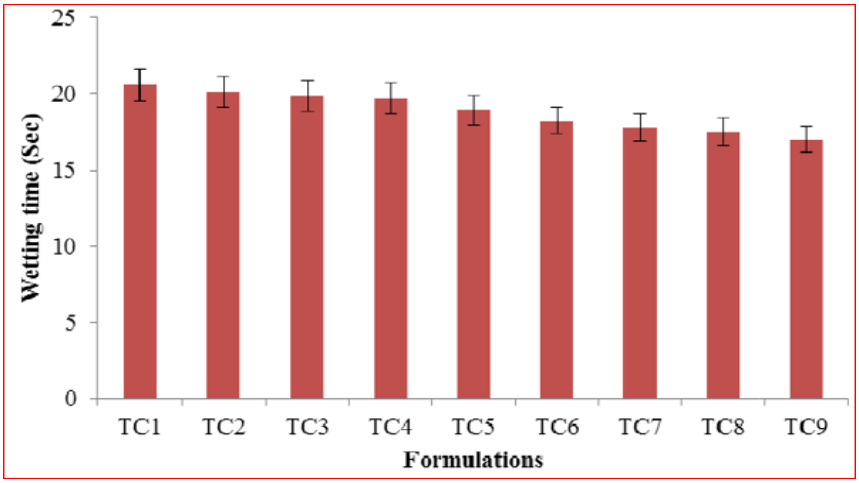

Figure 12: Wetting dissolving tablets factorial design Indomethacin

Table 18: Evaluation of Water absorption ratio of factorial design Indomethacin mouth dissolving tablets

Formulation	Water absorption ratio
TC1	68.87±0.05
TC2	69.21±0.04
TC3	70.15±0.06
TC4	70.53±0.07
TC5	70.98±0.09
TC6	71.29±0.06
TC7	73.47±0.02
TC8	74.25±0.08
TC9	75.31±0.07

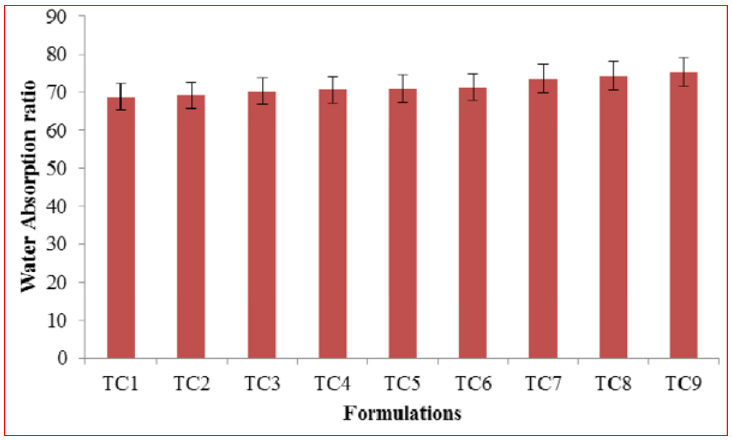

Figure 13: Water absorption ratio of factorial design Indomethacin mouth dissolving tablets

Table 19: Evaluation of in-vitro disintegration time of factorial design Indomethacin mouth dissolving tablets

Formulation	In vitro disintegration time (sec)
TC1	25.34±0.02
TC2	25.05±0.07
TC3	24.23±0.05
TC4	24.86±0.04
TC5	23.47±0.09
TC6	23.15±0.06
TC7	22.72±0.03
TC8	22.13±0.07
TC9	21.79±0.08

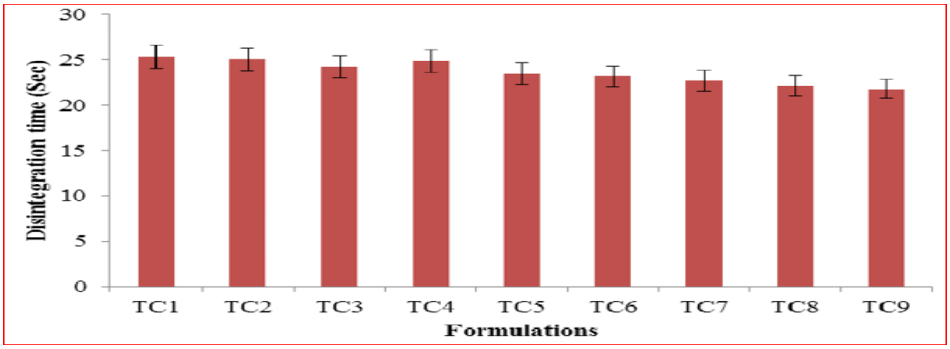

Figure 14: Disintegration time of factorial design Indomethacin mouth dissolving tablets

In-vitro drug release studies of factorial design of Indomethacin mouth dissolving tablets

in-vitro dissolution studies revealed that 97.61 to 100% of drug release from various formulations of factorial design of Indomethacin mouth dissolving tablets. The 50% of the drug was released from all formulation within 4 minutes. The rapid drug dissolution might be due to easy breakdown of particle by superdisintegrant action. From in vitro dissolution data, it was observed that formulation TC7 released Indomethacin 100% in 14 minutes. represents the log cumulative percent drug release and log cumulative percent drug remain in full factorial design Indomethacin mouth dissolving tablets respectively. From result it was observed that on increasing the concentration of Sodium starch glycolate disintegrates in formulation it decreases the release of drug. This may be due to gelling property of sodium starch glycolate. Hence the formulation TC7 considered best among other formulations.

Table 20: In-vitro dissolution study of full factorial design Indomethacin mouth dissolving tablets

Time in mins	Sq. rt. of Time	Log Time	Cumulative percent drug release								
			TC1	TC2	TC3	TC4	TC5	TC6	TC7	TC8	TC9
0	0	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	1.41	0.30	28.32	28.75	27.18	29.47	29.35	28.63	30.24	30.13	29.51
4	2	0.60	50.68	51.34	50.42	53.39	52.57	52.71	55.16	54.27	53.46
8	2.82	0.90	75.25	74.49	73.24	77.82	76.29	75.38	77.43	76.52	75.67
12	3.46	1.07	85.42	86.15	82.56	86.28	87.92	85.27	89.73	86.32	84.15
14	3.74	1.14	98.14	99.05	97.65	99.31	98.24	97.61	100.00	99.21	98.49

Table 21: Log cumulative percent drug release from full factorial design Indomethacin mouth dissolving tablets

Time in mins	Sq. rt. of Time	Log Time	Log cumulative percent drug release								
			TC1	TC2	TC3	TC4	TC5	TC6	TC7	TC8	TC9
0	0	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	1.41	0.30	1.45	1.45	1.43	1.46	1.46	1.45	1.48	1.47	1.46
4	2	0.60	1.70	1.71	1.70	1.72	1.72	1.72	1.74	1.73	1.72
8	2.82	0.90	1.87	1.87	1.86	1.89	1.88	1.87	1.88	1.88	1.87
12	3.46	1.07	1.93	1.93	1.91	1.93	1.94	1.93	1.95	1.93	1.92
14	3.74	1.14	1.99	1.99	1.98	1.99	1.99	1.98	2.00	1.99	1.99

Table 22: Log cumulative percent drug relmain from full factorial design Indomethacin mouth dissolving tablets

Time in mins	Sq. rt. of Time	Log Time	Cumulative percent drug remains								
			TC1	TC2	TC3	TC4	TC5	TC6	TC7	TC8	TC9
0	0	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	1.41	0.30	1.85	1.85	1.86	1.84	1.84	1.85	1.84	1.84	1.84
4	2	0.60	1.69	1.68	1.69	1.66	1.67	1.67	1.65	1.66	1.66
8	2.82	0.90	1.39	1.40	1.42	1.34	1.37	1.39	1.35	1.37	1.38
12	3.46	1.07	1.16	1.14	1.24	1.137	1.08	1.16	1.01	1.13	1.20
14	3.74	1.14	0.26	0.02	0.37	0.16	0.24	0.37	0.00	-0.10	0.17

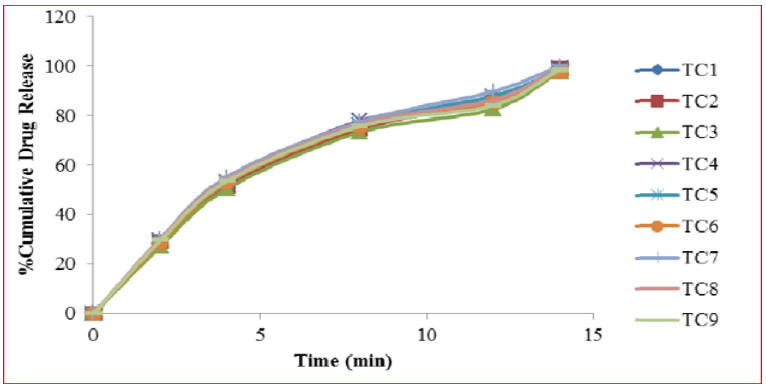

Figure 15: In-vitro drug release profile of full factorial design Indomethacin mouth dissolving tablets according to zero order release

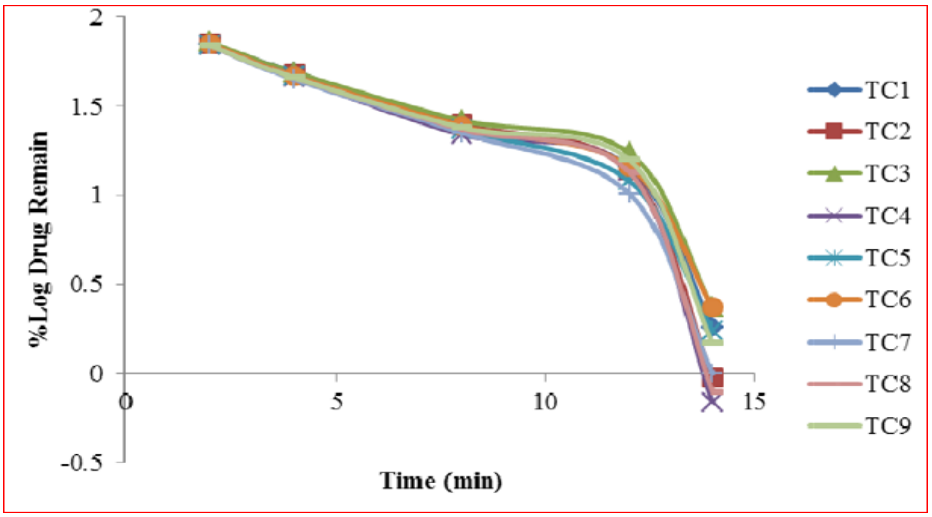

Figure 16: In-vitro drug release profile of full factorial design Indomethacin mouth dissolving tablets according to first order release

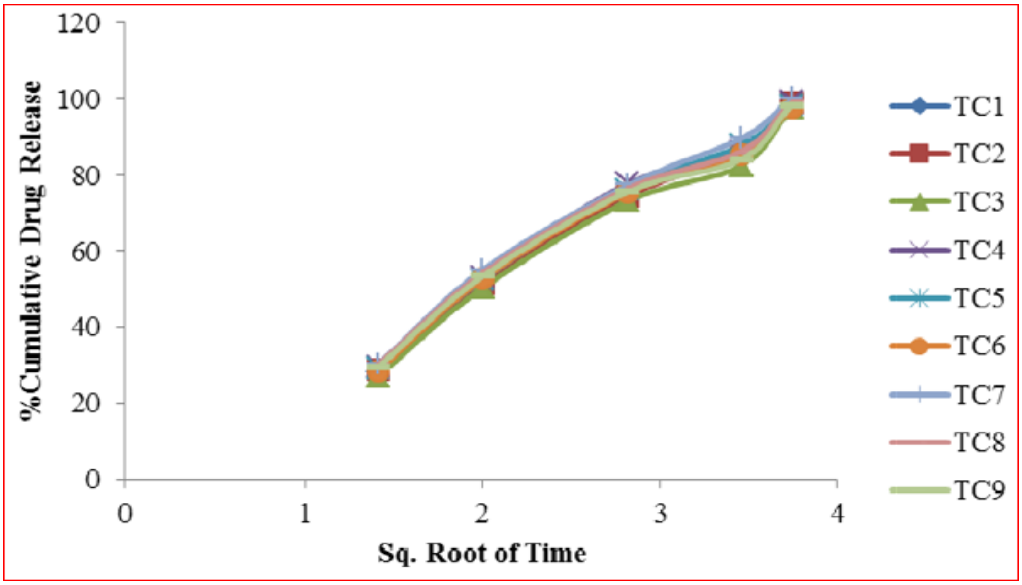

Figure 17: In-vitro drug release profile of full factorial design Indomethacin mouth dissolving tablets according to higuchi's model

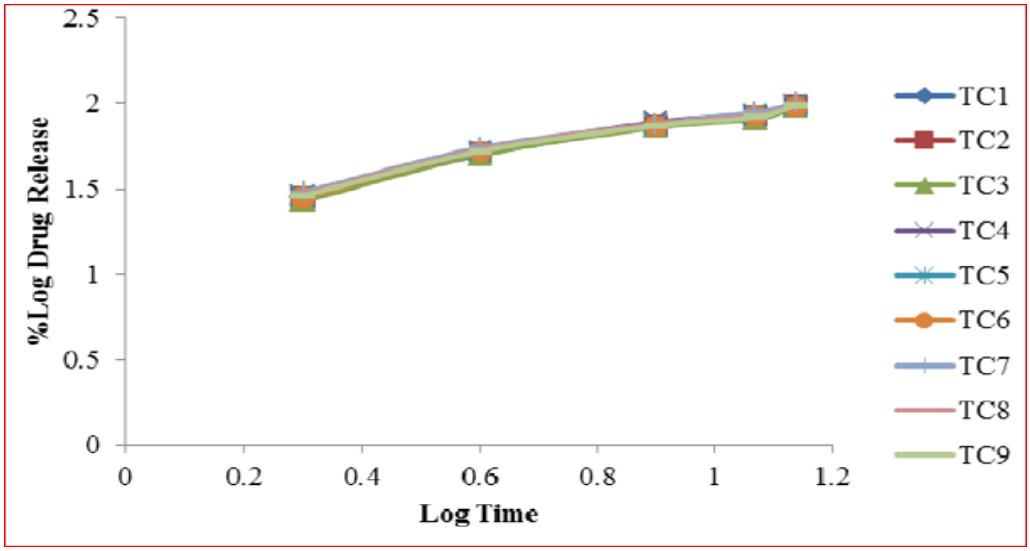

Figure 18: In-vitro drug release profile of full factorial design Indomethacin mouth dissolving tablets according to korsmeyer and peppas model

Kinetics of in vitro drug release of full factorial design Indomethacin mouth dissolving tablets

The formulations of full factorial design Indomethacin tablets were subjected to four model fitting analysis namely, zero order (Fig 15), first order (Fig 16), Higuchi (Fig 17) and Korsmeyer-peppas model (Fig 18). Table 26, indicate that all the formulations follow the Higuchi kinetics as the co-efficient of regression (R^2) was more near to unity as compared to the regression value of zero order and first order model. Among all the formulations it was observed that R^2 value of formulation TC7 is more near to one than other formulations. On the basis of this parameter, TC7 was considered best formulation.

Table 23: Kinetics of in vitro drug release profile of full factorial design Indomethacin mouth dissolving tablets

Formulation code	Zero order	First order	Higuchi	Korsmeyer and Peppas Model	
	R^2	R^2	R^2	n	R^2
TC1	0.904	0.914	0.984	0.617	0.983
TC2	0.907	0.875	0.987	0.613	0.978
TC3	0.908	0.902	0.978	0.618	0.972
TC4	0.889	0.858	0.976	0.603	0.971
TC5	0.894	0.935	0.986	0.606	0.977
TC6	0.893	0.931	0.979	0.602	0.971
TC7	0.888	0.919	0.988	0.590	0.976
TC8	0.889	0.866	0.979	0.586	0.971
TC9	0.891	0.880	0.974	0.593	0.972

Model fitting analysis of formulations of full factorial design Indomethacin mouth dissolving tablets

The values of n in Korsmeyer- papas model suggested that all formulations of full factorial design Indomethacin tablets follow Non Fickian Anomalous.

Table 24: Model fitting analysis of all the formulation of full factorial design Indomethacin mouth dissolving tablets

Formulation code	Value of n	R^2 Value	Mode of transport
TC1	0.617	0.983	Non Fickian Anamolous
TC2	0.613	0.978	Non Fickian Anamolous
TC3	0.618	0.972	Non Fickian Anamolous
TC4	0.603	0.971	Non Fickian Anamolous
TC5	0.606	0.977	Non Fickian Anamolous
TC6	0.602	0.971	Non Fickian Anamolous
TC7	0.590	0.976	Non Fickian Anamolous
TC8	0.586	0.971	Non Fickian Anamolous
TC9	0.593	0.972	Non Fickian Anamolous

CONCLUSION:

It was deduced that MDTs of Indomethacin formulated by direct compression method. The superdisintegrants were used in formulation to ameliorate the disintegration of tablets. It produces better patient compliance and effective therapy of tablets. Also, the bitter drug can be easily formulated as mouth dissolving tablets by masking their taste using aspartame as taste masking agent. It was also found that the superdisintegrants are effective at an optimum concentration, on increasing the ratio of Crospovidone and Sodium starch glycolate concentration above their optimum concentration this enhance the gelling effects of formulation. The formulation TC7 exhibited better results as compared to other formulations. Further these formulations can be select for in vivo study.

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