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Formulation and Evaluation of Solid Dispersion Incorporated Fast Disintegrating Tablets of Tenoxicam Using Design of Experiment

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ABSTRACT

The aim of the present work is to develop fast dissolving tablets from the solid dispersion of Tenoxicam for enhancement of solubility. The solid dispersions of Tenoxicam were prepared with Kollidon CL, PVP K30 and Poloxamer 127, in 1:1:1, 1:2:1 and 1:3:1 by using solvent evaporation method. The prepared solid dispersions were analyzed for all the physical parameters, drug: carrier interactions like FTIR, SEM, XRD. Solid dispersions showed a better dissolution compared to the pure drugs and among all the other formulations SD9 shows high percentage drug release i.e. 99.11 ± 5.17% for 90 min and selected as an optimized formulation for the preparation of fast disintegrating tablets of Tenoxicam. Gellan Gum, Fenugreek Seed Mucilage and L-HPC (low, middle and high concentrations) used in the preparation of fast disintegrating tablets prepared by direct compression method using 3^3 Response surface method. The post compression parameters of all the prepared tablets were within the limits. TF13 was selected as optimized formulation based on its highest disintegration time 36 sec and drug release 99.68 ± 1.52% for 10 min. Drug-excipients characterization also revealed that there is no interaction. Hence it concluded that solid dispersions incorporated fast disintegrating tablets is very useful approach for immediate release of Tenoxicam in the efficient management of inflammation and pain.

Keywords: Tenoxicam, NSAID's, Solid dispersion, Fast disintegrating tablets, Gellan gum.

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INTRODUCTION

Oral route is the most frequently used route of drug administration with convenient and cost-effective. [1] Tablet is one of the most popular among all the oral dosage forms existing today because of its convenience of self-administration, compactness and easy manufacturing. Fast dissolving dosage forms can be disintegrated, dissolved, or suspended by saliva in the mouth. [2] But the oral formulation with poor solubility is a greater limitation for the formulation scientists, solubility enhancement should be the prime concern for a dosage form to get ideal bioavailability. [3] Although salt formation, solubilization, particle size reduction has commonly used to increase dissolution rate and thereby oral absorption and bioavailability of low water-soluble drugs 2-4, there is practical limitation to these techniques. [4] Among all the techniques solid dispersions is one of the promising techniques. [5] Solid

dispersions (SDs) have traditionally been used as an effective method to improve the dissolution properties and bioavailability of poorly water-soluble drugs. [6] Fast dissolving tablets are useful for patients with difficulties swallowing conventional tablets, for example pediatric patients and patients under chemotherapy treatment. [7] To allow fast dissolving of dosage forms in the mouth, these delivery systems comprise either very porous and soft-molded matrices or compression into tablets with very low compression force. [8] Tenoxicam belongs to the well-known group of Cox-II inhibitors, oxicams, it is a well-established, potent nonsteroidal anti-inflammatory agent with analgesic actions achieved by inhibiting prostaglandin synthesis. [9] Tenoxicam has been found to be approximately 99% protein bound with a mean elimination half-life of 67 h, which allows the administration of a daily single oral dose of 20 mg. [10-11] In the present work an attempt has been made to improve the solubility of Tenoxicam by solid dispersions using Solvent evaporation method along with the aid of novel polymers and further developed into fast disintegrating tablets.

Table 1: Preliminary solubility studies of Tenoxicam in different polymers

Physical Mixture (1:1)	Solubility (mg/ml)*
Tenoxicam Pure drug	0.068 ± 0.14
Drug + Kolliwax GMS II	0.682 ± 0.11
Drug + Poloxamer127	0.93 ± 0.04
Drug + Aerosil 200	0.744 ± 0.09
Drug + PEG 6000	0.558 ± 0.20
Drug + PVP K 30	0.868 ± 0.14
Drug + Soluplus	0.62 ± 0.08
Drug + Kollidon CL	1.116 ± 0.21
Drug + Urea	0.496 ± 0.07

Fig. 1: Optimized formulation of Tenoxicam solid dispersions

MATERIALS AND METHODS

Materials

Tenoxicam pure drug was generous gift from Aurobindo Pharma Ltd., Hyderabad, India. Kollidon CL and PEG 6000 were obtained from Signet Chemical Corp. Pvt. Ltd., Mumbai. Poloxamer 127 and Soluplus were gifted by BASF, Germany. HPMC and PVP K-30 were gifted by Dow Chemicals, USA. Gellan Gum, Fenugreek seed mucilage and L-HPC were obtained from Yarrow chemicals, Mumbai. Mannitol, Avicel PH 101, Aspartame, Aerosil, Magnesium Stearate and Talc were obtained from SD fine chemicals. All other chemicals used were of analytical grade.

Preliminary solubility studies of Tenoxicam

Solubility measurement of Tenoxicam was performed according to a published method given by Higuchi and Connors in 1965. [12] An excess amount of Tenoxicam was added to 25 ml of aqueous solution of water-soluble carriers like PEG 6000, Kollidon CL, Soluplus, Aerosil 200, Poloxamer 127, HPMC, Urea and PVPK-30 in screw capped bottles. Samples were shaken for the 24 hours at room temperature. Subsequently, the suspensions were filtered through a Whatman filter paper no. 1. Filtered solution was diluted with methanol and analyzed for the Tenoxicam at UV 369 nm.

Preparation of Tenoxicam solid dispersion by the solvent evaporation method

The calculated amount of Tenoxicam and the employed polymers of Poloxamer 127, PVPK-30, Kollidon CL and SLS in different drug, polymer and surfactant ratios of 1:1:1, 1:2:1 and 1:3:1 (shown in Table 2) are weighed and mixed together in a porcelain dish. Nine different formulae were prepared by the solvent evaporation method. The mixture was dissolved in small amount of methanol. Then the solvent was evaporated in oven at temperature 50°C until complete evaporation. The solid dispersions prepared were pulverized in a mortar and sieved. The fraction of the powder that passed through 45µm was stored in a desiccator and utilized for further study.

Table 2: Composition of Tenoxicam solid dispersions

Ingredients (mg)	SD1 (1:1:1)	SD2 (1:2:1)	SD3 (1:3:1)	SD4 (1:1:1)	SD5 (1:2:1)	SD6 (1:3:1)	SD7 (1:1:1)	SD8 (1:2:1)	SD9 (1:3:1)
Tenoxicam (mg)	20	20	20	20	20	20	20	20	20
Poloxamer127	20	40	60	-	-	-	-	-	-
PVP K 30 (mg)	-	-	-	20	40	60	-	-	-
Kollidon CL (mg)	-	-	-	-	-	-	20	40	60
SLS (mg)	20	20	20	20	20	20	20	20	20
Ethanol (ml)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

Evaluation of Tenoxicam solid dispersions

Solid dispersions obtained by solvent evaporation method were tested for their percentage practical yield, drug content, FTIR, SEM, XRD, *in vitro* release and stability studies.

Percentage Practical Yield

Percentage practical yield was calculated to know about percent yield or efficiency of any method and help in selection of appropriate method of production. [13]

Drug content

Solid dispersions equivalent to 20 mg of Tenoxicam was weighed accurately and dissolved in 100 ml of

methanol. The solution was filtered, diluted suitable and drug content was analysed at λ_{max} 369 nm against blank by UV spectrometer. [14]

In vitro Dissolution study of solid dispersion

The USP dissolution test type II apparatus (Electrolab TDT- 06 N, India) was used. Number of samples equivalent to 20 mg of drug were dispersed into the dissolution vessel containing 900 mL of with pH 7.4 phosphate buffer at 37°C and stirred at 50 rpm. Samples were withdrawn periodically, filtered and replaced with a fresh dissolution medium. After filtration through 0.45µm microfilter, concentration of Tenoxicam was determined spectrophotometrically at λ_{max} 369 nm. [15]

Characterization

FTIR studies

Using Shimadzu FTIR-8700 spectrophotometer, potassium bromide disc method is employed. [16]

Powder X-ray diffraction (XRD)

X-ray powder diffraction patterns were recorded on an X-ray powder diffraction system (Shimadzu, Japan) using copper target, a voltage of 40 Kv and a current of 30 mA. The scanning was done over 2 range of 5°C to 60°C. [17]

SEM studies

Surface morphology of layered sample was inspected by using SEM (Hitachi, Japan). Small amount of powder was manually dispersed onto a carbon tab (double adhesive carbon coated tape) adhered to an aluminum stub. These sample stubs were coated with thin layer (30 Å) of gold by employing POLARON-E 3000 sputter coater. Samples remained examined by SEM & photographed under various magnifications with direct data capture images onto a computer. [18]

DSC studies

Differential Scanning Calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. [19]

Stability studies

Prepared solid dispersions were placed inside sealed 40cc HDPE container with child resistant cap under controlled temperature environment inside stability chamber (Thermo Lab, India) with relative humidity of 75% ± 5% RH and temperature 40°C ± 2°C for stability studies. Samples were removed after 1, 2 and 3 months and evaluated for % drug content and *in vitro* dissolution studies and compared with those results. [20]

Preparation of Tenoxicam fast disintegrating tablets

Twenty-seven formulations (TF1-TF27) for active layer were prepared by direct compression method using 3^3 Response surface method (3 variables and 3 levels of superdisintegrants) by using Design of experiment software with superdisintegrants like Gellan Gum, Fenugreek Seed Mucilage and L-HPC. All the formulations were varied in concentration of superdisintegrants, magnesium stearate constituted in all the formulations. These materials were screened through #60 and mixed together in motor by using pestle. Final mixtures were compressed by using 8 mm diameter flat punches on an eight-station rotary tablet press. Formulations were depicted in Table 5. The prepared tablets were subjected to dissolution studies. [21]

Response surface methodology

Study type: Response surface
Design type: central composite
Design mode: quadratic

Design Summary

		27	
Study Type	Response Surface	Runs	
Initial Design	3 Level Factorial	Blocks	No Blocks
Design Model	Quadratic		

Factor	Name	Units	Type	Low Actual	High Actual	Low Coded	High Coded	Mean	Std. Dev.
A	GELLAN GUM	%	Numeric	7.00	9.00	-1.000	1.000	8.000	0.802
B	FENUGREEK SEI	%	Numeric	13.00	15.00	-1.000	1.000	14.000	0.802
C	L-HPC	%	Numeric	19.00	21.00	-1.000	1.000	20.000	0.802

Response	Name	Units	Obs	Analysis	Minimum	Maximum	Mean	Std. Dev.	Ratio
Y1	%CDR	%	0	Polynomial	No Data	No Data	No Data	No Data	N/A
Y2	DT	%	0	Polynomial	No Data	No Data	No Data	No Data	N/A

Twenty-seven formulations (TF1-TF27) were prepared by direct compression method using 3^3 Response surface method where 3^3 indicates 3 variables and 3 levels of superdisintegrants like Gellan Gum, Fenugreek Seed Mucilage and L-HPC (low, middle and high concentrations) by using Design of experiment software. [21-22]

Pre-compression evaluation tests

Preformulation studies: Prior to compression, solid dispersions were evaluated for their characteristic pre-compression parameters, such as bulk density, tapped density, Hausner ratio, Car's compressibility index and angle of repose. [23-24]

Post compression evaluation tests

Post compression parameters like Weight Variation, Thicknesses, Hardness, Friability, Content Uniformity and *in vitro* disintegration time studies were performed. [25-26]

Table 3: Percent Practical yield and drug content for Tenoxicam solid dispersions

S. No	Formulation	% Practical Yield	% Drug content
1	SD1	93.26 ± 0.19	90.44 ± 0.11
2	SD2	92.49 ± 0.12	93.44 ± 0.25
3	SD3	94.77 ± 0.33	92.11 ± 0.31
4	SD4	96.16 ± 0.11	94.55 ± 0.27
5	SD5	91.44 ± 0.41	95.34 ± 0.07
6	SD6	96.68 ± 0.08	96.11 ± 0.49
7	SD7	97.19 ± 0.04	95.77 ± 0.70
8	SD8	97.99 ± 0.27	97.52 ± 0.44
9	SD9	98.87 ± 0.51	99.09 ± 0.55

Table 4: Evaluation parameters of SD9 stored at 40 ± 2°C / 75 ± 5% RH

Retest time for optimized formulation	% Drug content	*In-vitro* drug release (%)
0 days	98.87	99.09
30 days	98.55	98.44
60 days	97.49	97.76
90 days	96.32	96.34

Table 5: Formulation trials of Tenoxicam fast disintegrating tablet

F. No	Tenoxicam	Gellan gum	Fenugreek Seed Mucilage	L-HPC	Aspartame	Mannitol	MCC	Total
TF1	100	14	26	38	15	60	41	300
TF2	100	18	26	38	15	60	37	300
TF3	100	14	30	38	15	60	37	300
TF4	100	16	28	38	15	60	37	300
TF5	100	14	26	42	15	60	37	300
TF6	100	18	26	42	15	60	33	300
TF7	100	14	30	42	15	60	33	300
TF8	100	16	30	42	15	60	31	300
TF9	100	14	30	42	15	60	33	300
TF10	100	18	28	40	15	60	33	300
TF11	100	16	26	40	15	60	37	300
TF12	100	16	30	40	15	60	33	300
TF13	100	18	30	42	15	60	29	300
TF14	100	16	28	42	15	60	33	300
TF15	100	16	28	40	15	60	35	300
TF16	100	16	26	42	15	60	35	300
TF17	100	16	26	38	15	60	39	300
TF18	100	16	30	40	15	60	33	300
TF19	100	18	26	40	15	60	35	300
TF20	100	16	30	38	15	60	35	300
TF21	100	18	28	38	15	60	35	300
TF22	100	18	28	40	15	60	33	300
TF23	100	18	30	40	15	60	31	300
TF24	100	14	28	40	15	60	37	300
TF25	100	18	28	42	15	60	31	300
TF26	100	14	28	38	15	60	39	300
TF27	100	16	28	38	15	60	37	300

Note: Magnesium stearate and Talc were added in quantity of 3 mg each in all formulation

In vitro disintegration time

The USP device to rest disintegration was six glass tubes that are "3 long, open at the top, and held against 10" screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1liter beaker of buffer at 37 ± 2°C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5 cm from the bottom of the beaker.

In vitro Drug Dissolution Study

The dissolution of prepared Fast Disintegrating tablet formulations was carried out by using USP Dissolution apparatus Type II and Phosphate buffer pH 7.4 of media volume 900 ml by maintaining the temperature of 37 ± 0.2°C and the withdrawn samples are estimated at 369 nm.

Stability studies

The optimized formulation was subjected to stability studies at 40°C ± 75% RH for period of three months. Each tablet was individually wrapped in aluminum foil and packed in ambered colored bottle and put at a specified condition in a heating.

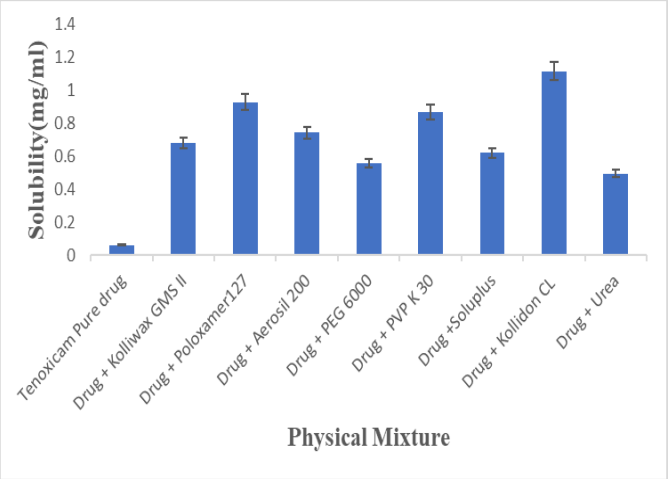


Fig. 2: Solubility studies of Tenoxicam physical mixture

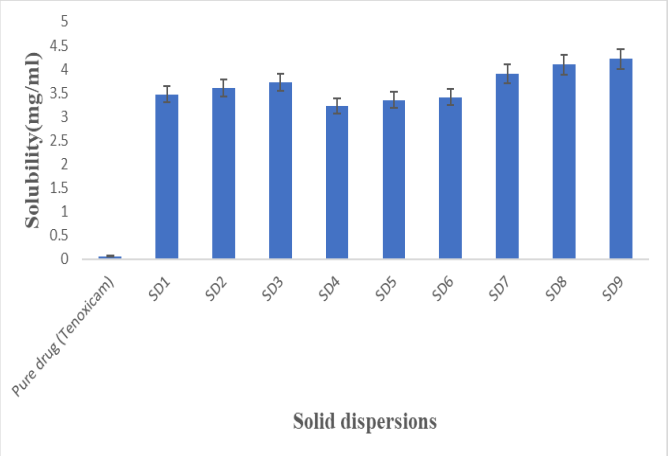


Fig. 3: Solubility studies of Tenoxicam solid dispersion

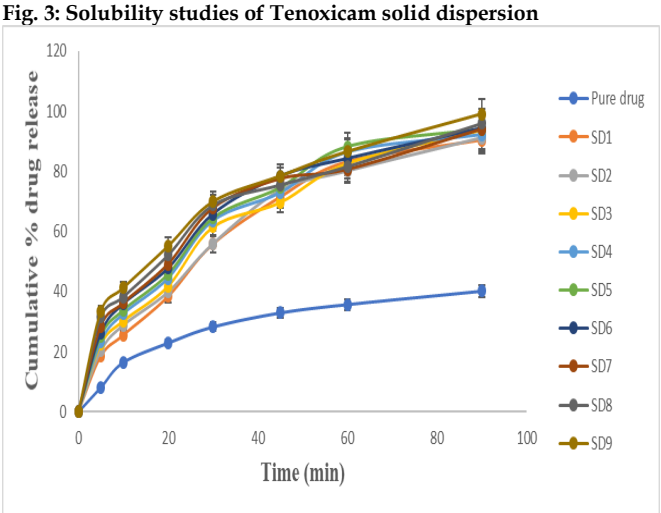


Fig. 4: *In vitro* dissolution profile of pure drug and different formulations of Tenoxicam solid dispersions (SD1-SD9)

RESULTS AND DISCUSSION

Preliminary solubility studies of Tenoxicam

Initially preliminary solubility analysis was carried out to select the appropriate water-soluble carriers for the preparation of solid dispersion in which Tenoxicam pure drug solubility was found to be 0.068 ± 0.14 mg/ml. From this study, drug and Kollidon CL in the

ratio of 1:1 exhibits highest drug solubility of 1.116 ± 0.21 mg/ml [27], almost 18-fold increase compared to that of pure drug. Among all the water-soluble carriers used PEG 6000, Soluplus, Urea, HPMC and Aerosil 200 showed low solubility and therefore are not included in the preparation of Tenoxicam solid dispersions (Table 1).

Preparation of Tenoxicam solid dispersions

Solid dispersions of Tenoxicam were prepared by solvent evaporation method using different carriers like PEG 6000, Kollidon CL, Soluplus, Aerosil 200, Poloxamer 127, HPMC, Urea and PVPK-30 in three different drug: polymer: surfactant (SLS) ratios of 1:1:1, 1:2:1 and 1:3:1. Total 9 formulations were prepared; the mixture was dissolved in the least amount of methanol as a common solvent (Table 2). Then the solvent was evaporated in oven at temperature 50°C till complete evaporation. The resultant solid dispersion was scraped out with a spatula. Solid dispersions were pulverized in a mortar and pestle and passed through a 45µm sieve before packing in an airtight container, stored in a desiccator and used for further investigations. All the solid dispersions prepared were found to be fine and free flowing powers (Figure 1).

Evaluation parameters

Solubility studies of Tenoxicam solid dispersions

Tenoxicam solid dispersions were prepared by solvent evaporation method with their respective carriers. After preparation of solid dispersion solubility analysis was carried out. The formulation (SD9) with Soluplus in the ratio of 1:3 and with SLS shown highest solubility i.e. 4.216 ± 0.19 mg/ml, almost 68-fold compared to that of the pure drug (Pure drug solubility is 0.068 ± 0.14 mg/ml. The results are given as graphical representation in Figure 2 and 3.

Percent Practical yield and drug content

The formulation SD9 was found to have highest percent practical yield and percent drug content of 98.87% and 99.09% respectively when compared with other formulations. The results are given in Table 3.

In vitro dissolution studies

The drug release data obtained for formulations SD1-SD9 which represent the cumulative percent drug released as a function of time for all formulations. *In vitro* studies reveal that there is marked increase in the dissolution rate of Tenoxicam from all the solid dispersions when compared to pure Tenoxicam itself. From the *in vitro* drug release profile, it can be seen that formulation SD9 containing Tenoxicam, Kollidon CL and SLS in 1:3:1 ratio shows higher dissolution rate of 99.11 ± 5.17 at 90 min compared with other formulations. The graphical representation of solid dispersions of SD1-SD9 with pure drug is shown in Figure 4.

Characterization

FTIR studies

The IR spectra are shown in Figure 5, 6 and 7. Pure tenoxicam (A) exhibited characteristic peaks at 3126 cm^{-1} and 3088 cm^{-1} (N-H and O-H stretching), 1635 cm^{-1} (aromatic C=C stretching), 1521 $cm^{-1}$and 1510 cm^{-1} (Amide – C = O, C=N), 1440 cm^{-1} (C-H deformation), 1369 cm^{-1} (-CH_3 deformation). The optimized formulation of solid dispersion also exhibited the same characteristic peaks indicating retention of chemical identity of tenoxicam. Hence, there was no interaction between the drug and the carriers used to prepare the dispersions in the study.

Table 6: Physical properties of prepared powder blends of fast disintegrating tablets

Formulation	Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose(θ)	Carr's index (%)	Hausner ratio
TF1	0.52 ± 0.15	0.51 ± 0.56	22.56 ± 0.27	09.41 ± 0.49	1.13 ± 0.03
TF2	0.54 ± 0.34	0.50 ± 0.28	23.30 ± 0.17	11.48 ± 0.24	1.13 ± 0.05
TF3	0.50 ± 0.68	0.68 ± 0.02	25.56 ± 0.25	10.23 ± 0.39	1.15 ± 0.04
TF4	0.56 ± 0.22	0.69 ± 0.17	24.67 ± 0.36	11.31 ± 0.13	1.13 ± 0.09
TF5	0.60 ± 0.76	0.54 ± 0.34	25.56 ± 0.31	09.62 ± 0.49	1.12 ± 0.03
TF6	0.50 ± 0.21	0.63 ± 0.34	21.66 ± 0.22	10.22 ± 0.41	1.11 ± 0.02
TF7	0.53 ± 0.06	0.68 ± 0.23	25.34 ± 0.24	10.42 ± 0.31	1.14 ± 0.09
TF8	0.55 ± 0.39	0.62 ± 0.22	24.34 ± 0.43	09.62 ± 0.22	1.10 ± 0.03
TF9	0.59 ± 0.97	0.59 ± 0.33	21.67 ± 0.33	11.42 ± 0.86	1.13 ± 0.06
TF10	0.52 ± 0.28	0.63 ± 0.34	26.54 ± 0.16	11.90 ± 0.34	1.12 ± 0.03
TF11	0.53 ± 0.37	0.62 ± 0.24	23.89 ± 0.22	11.459 ± 0.62	1.13 ± 0.01
TF12	0.57 ± 0.19	0.67 ± 0.33	22.45 ± 0.43	10.11 ± 0.54	1.11 ± 0.03
TF13	0.59 ± 0.95	0.69 ± 0.56	21.09 ± 0.32	11.03 ± 0.45	1.13 ± 0.03
TF14	0.50 ± 0.57	0.60 ± 0.33	23.05 ± 0.25	09.31 ± 0.22	1.14 ± 0.09
TF15	0.52 ± 0.49	0.61 ± 0.02	25.06 ± 0.26	10.61 ± 0.42	1.11 ± 0.05
TF16	0.55 ± 0.37	0.52 ± 0.31	22.78 ± 0.44	09.69 ± 0.61	1.12 ±0.06
TF17	0.51 ± 0.77	0.67 ± 0.77	22.45 ± 0.43	11.27 ± 0.57	1.14 ± 0.01
TF18	0.53 ± 0.66	0.64 ± 0.35	25.09 ± 0.34	09.31 ± 0.59	1.13 ± 0.06
TF19	0.57 ± 0.44	0.61 ± 0.67	23.05 ± 0.23	11.09 ± 0.79	1.12 ± 0.02
TF20	0.53 ± 0.06	0.60 ± 0.16	25.06 ± 0.24	09.23 ± 0.83	1.11 ± 0.06
TF21	0.57 ± 0.11	0.60 ± 0.69	24.78 ± 0.13	08.29 ± 1.01	1.11 ± 0.04
TF22	0.56 ± 0.19	0.69 ± 0.07	25.34 ± 0.44	10.11 ± 0.74	1.10 ± 0.05
TF23	0.54 ± 0.18	0.67 ± 0.49	23.42 ± 0.32	11.34 ± 0.62	1.12 ± 0.09
TF24	0.57 ± 0.17	0.63 ± 0.49	22.99 ± 0.52	11.29 ± 0.82	1.11 ± 0.04
TF25	0.55 ± 0.13	0.67 ± 0.06	25.14 ± 0.34	10.20 ± 0.56	1.10 ± 0.04
TF26	0.52 ± 0.4	0.64 ± 0.37	24.09 ± 0.23	10.39 ± 1.07	1.12 ± 0.06
TF27	0.54 ± 0.47	0.66 ± 0.19	22.78 ± 0.46	09.13 ± 0.82	1.10 ± 0.04

Above parameters are communicated as Average ± Standard Deviation; (n=6)

Table 7: Physico-chemical parameters of fast disintegrating tablets of Tenoxicam

F. No	*Weight variation (mg)	#Thickness (mm)	#Hardness (Kg/Cm²)	#Friability (%)	#Content uniformity (%)	DT (Sec)
TF1	298.29 ± 1.23	4.1 ± 0.29	5.4 ± 0.13	0.74 ± 0.03	94.11 ± 0.37	51 ± 1.23
TF2	300.28 ± 0.87	4.3 ± 0.59	5.1 ± 0.062	0.75 ± 0.02	97.23 ± 0.3	72 ± 1.51
TF3	301.37 ± 0.56	4.3 ± 0.49	5.2 ± 0.09	0.78 ± 0.01	96.13 ± 0.97	65 ± 1.40
TF4	299.97 ± 0.03	4.2 ± 0.55	5.3 ± 0.19	0.79 ± 0.01	95.23 ± 0.27	55 ± 1.19
TF5	301.17 ± 0.46	4.2 ± 0.34	4.9 ± 0.03	0.82 ± 0.01	97.97 ± 0.93	65 ± 1.25
TF6	298.96 ± 0.43	4.3 ± 0.27	5.0 ± 0.01	0.84 ± 0.03	97.45 ± 0.75	48 ± 1.87
TF7	299.37 ± 0.35	4.3 ± 0.99	5.7 ± 0.13	0.63 ± 0.03	94.11 ± 0.37	57 ± 1.63
TF8	300.27 ± 0.23	4.1 ± 0.43	4.7 ± 0.45	0.66 ± 0.02	97.23 ± 0.93	68 ± 1.37
TF9	302.44 ± 0.36	4.4 ± 0.21	3.4 ± 0.02	0.53 ± 0.03	96.13 ± 0.27	56 ± 1.19
TF10	300.27 ± 0.24	4.2 ± 0.20	3.9 ± 0.42	0.76 ± 0.05	95.23 ± 0.27	58 ± 1.24
TF11	301.37 ± 0.42	4.2 ± 0.47	3.8 ± 0.02	0.74 ± 0.03	97.97 ± 0.63	63 ± 1.19
TF12	302.37 ± 0.35	4.3 ± 0.95	3.5 ± 0.06	0.73 ± 0.02	97.45 ± 0.44	56 ± 1.40
TF13	300.66 ± 0.29	4.3 ± 0.49	4.9 ± 0.32	0.52 ± 0.02	99.45 ± 0.48	36 ± 1.73
TF14	299.72 ± 0.30	4.1 ± 0.26	3.4 ± 0.22	0.76 ± 0.05	96.98 ± 0.93	55 ± 1.87
TF15	300.31 ± 0.24	4.4 ± 0.54	3.8 ± 0.22	0.43 ± 0.08	96.45 ± 0.41	68 ± 1.35
TF16	298.37 ± 0.37	4.2 ± 0.34	3.4 ± 0.22	0.67 ± 0.02	96.45 ± 0.41	54 ± 1.81
TF17	299.22 ± 0.46	4.5 ± 0.73	4.0 ± 0.39	0.72 ± 0.89	96.34 ± 0.63	53 ± 1.56
TF18	301.41 ± 0.19	4.5 ± 0.57	3.7 ± 0.32	0.89 ± 0.03	96.29 ± 0.71	52 ± 1.12
TF19	302.22 ± 0.32	4.0 ± 0.63	3.9 ± 0.12	0.52 ± 0.01	97.18 ± 0.17	57 ± 1.33
TF20	299.71 ± 0.24	4.0 ± 0.27	5.0 ± 0.1	0.55 ± 0.02	96.27 ± 0.9	58 ± 132
TF21	298.27 ± 0.43	4.2 ± 0.93	5.1 ± 0.36	0.63 ± 0.03	96.78 ± 0.42	55 ± 1.27
TF22	300.27 ± 0.14	4.2 ± 0.72	5.2 ± 0.92	0.72 ± 0.01	96.14 ± 0.79	60 ± 1.61
TF23	300.26 ± 0.13	4.0 ± 0.57	3.8 ± 0.27	0.62 ± 0.02	96.29 ± 0.31	68 ± 1.49
TF24	301.10 ± 0.57	4.3 ± 0.67	3.7 ± 0.21	0.66 ± 0.01	97.16 ± 0.19	53 ± 1.31
TF25	299.12 ± 0.66	4.3 ± 0.92	3.6 ± 0.19	0.58 ± 0.02	96.23 ± 0.02	51 ± 1.39
TF26	300.46 ± 0.89	4.1 ± 0.47	3.9 ± 0.27	0.69 ± 0.01	97.34 ± 0.27	69 ± 1.40
TF27	300.69 ± 0.15	4.4 ± 0.63	4.2 ± 0.49	0.89 ± 0.03	97.10 ± 0.44	53 ± 1.77

*Values are expressed in mean ± SD : (n=20); #Values are expressed in mean ± SD : (n=3)

Table 8: Stability studies of optimized formulation

Retest Time for Optimized formulation (TF13)	#Hardness (Kg/Cm²)	Disintegration test (Sec)	*In-vitro* drug release profile (%)
0 days	4.9 ± 0.45	36 ± 1.55	99.68 ± 1.22
30 days	4.9 ± 0.25	36 ± 0.39	99.68 ± 1.13
60 days	4.9 ± 0.17	36 ± 0.24	99.50 ± 1.25
120 days	4.9 ± 0.29	36 ± 0.19	99.18 ± 1.37
180 days	4.9 ± 0.15	37 ± 0.12	99.48 ± 1.22

*Values are expressed in mean ± SD :(n=6)

X-Ray Diffraction patterns

The Tenoxicam solid dispersions were studied for XRD to know whether the solid dispersions are crystalline or amorphous. The presence of numerous distinct peaks in the XRD spectrum of pure Tenoxicam indicates that Tenoxicam was present as a crystalline material (Figure 8). On the other hand, the spectrum of optimized formulation SD9 was characterized by the complete absence of any diffraction peak, which is characteristic of an amorphous compound (Figure 9). The enhancement in the dissolution rate of the drug from the drug- Kollidon CL -SLS solid dispersion is because of marked reduction in the crystallinity of the drug.

DSC studies

The DSC thermo grams of Pure Tenoxicam showed in (Figure 10), sharp endothermic peak at melting point 209°C, indicating that the drug is highly crystalline. The absence of drug peak in the solid dispersion formulation indicating the drug was converted into an amorphous form. As the intensity of the endotherm was markedly decreased in the drug - Kollidon CL with SLS solid dispersion, the faster dissolution rate of the drug from the solid dispersion is attributed to the reduction in the crystallinity of the drug. Crystallization inhibition is attributed to the entrapment of the drug molecules in the polymer matrix during solvent evaporation.

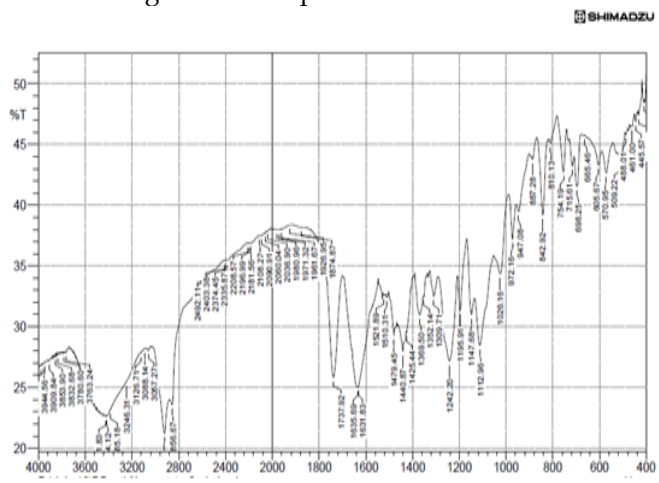


Fig. 5: FTIR Spectrum of Tenoxicam pure drug

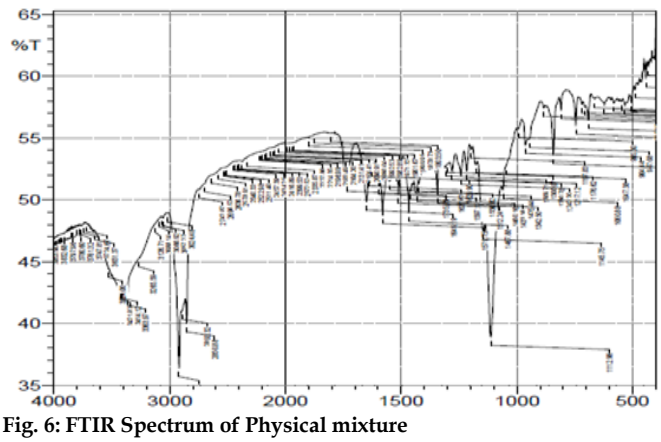


Fig. 6: FTIR Spectrum of Physical mixture

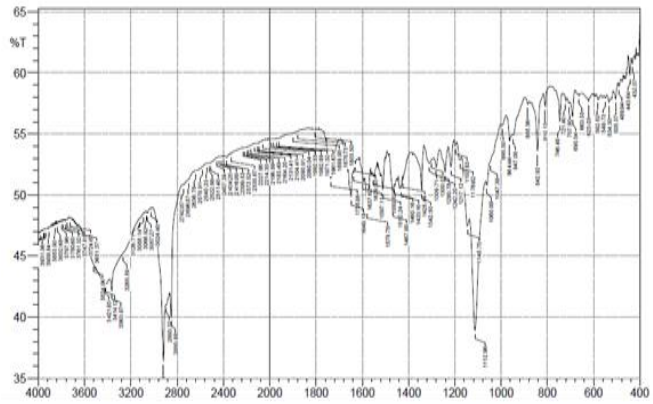


Fig. 7: FTIR Spectrum of Tenoxicam optimized formulation SD9

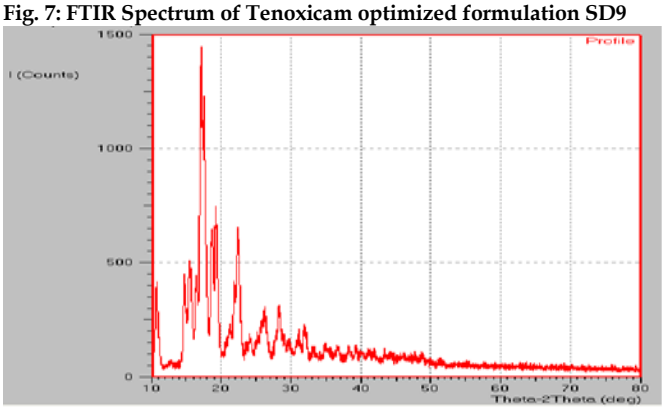


Fig. 8: X-Ray powder diffractogram of Tenoxicam pure drug

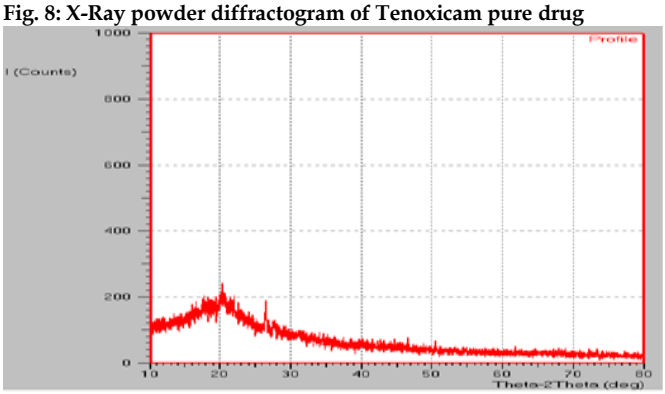


Fig. 9: X-Ray powder diffractogram of Tenoxicam optimized formulation

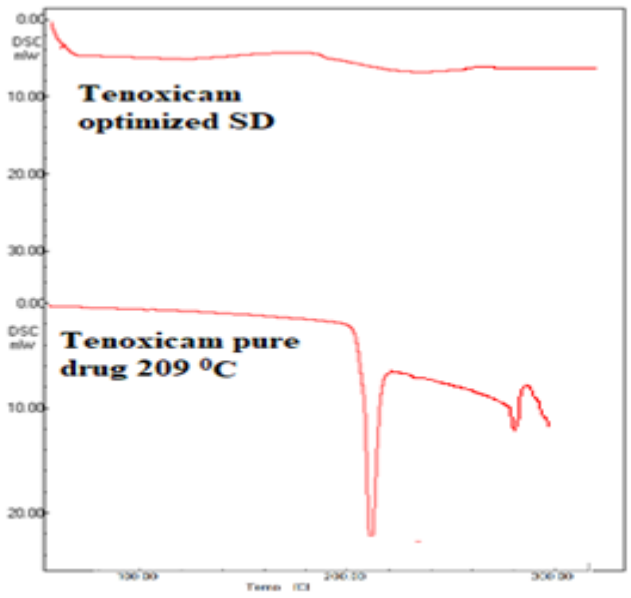
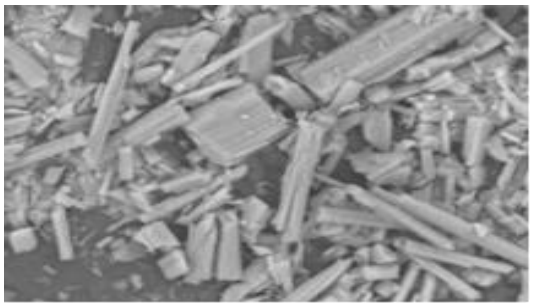
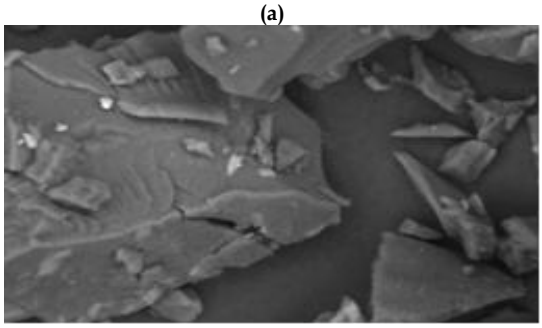


Fig. 10: DSC thermograms of Tenoxicam pure drug and Optimized formulation.



(a)



(b)

Fig. 11: SEM photographs of Tenoxicam pure drug (a) and optimized formulation (b.)

Fig. 12: Tenoxicam Tablets

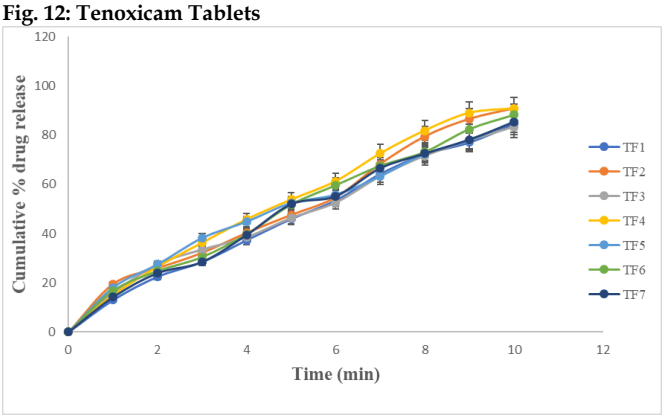


Fig. 13: *In vitro* Drug Release Profile of Fast Disintegrating Tablets of Tenoxicam TF1-TF7

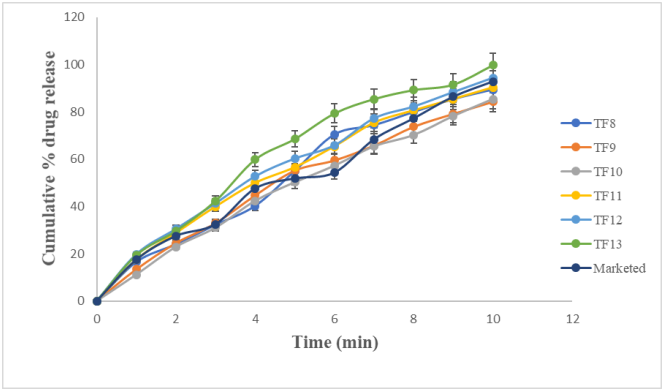


Fig. 14: *In vitro* Drug Release Profile of Fast Disintegrating Tablets of Tenoxicam TF8-TF13

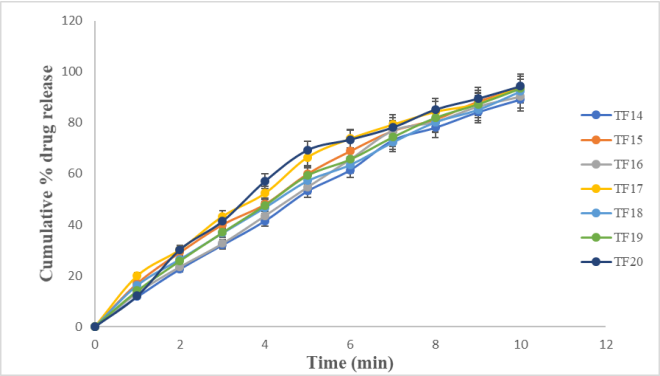


Fig. 15: *In vitro* **Drug Release Profile of Fast Disintegrating Tablets of Tenoxicam TF14-TF20**

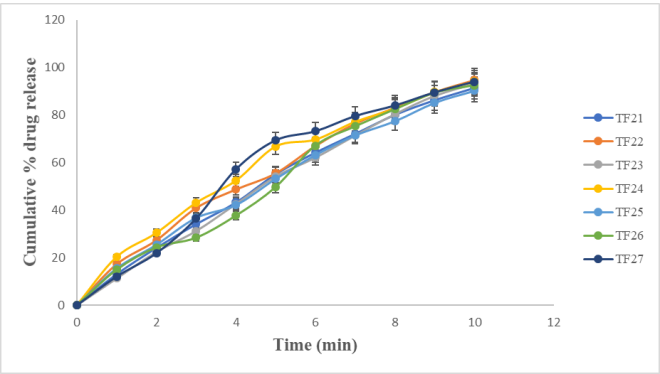


Fig. 16: *In vitro* **Drug Release Profile of Fast Disintegrating Tablets of Tenoxicam TF21-TF27**

SEM Studies

SEM photographs for Tenoxicam pure drug (a) and optimized formulation SE 9(b) are shown in Figure 11. The drug crystals seemed to be smooth-surfaced, irregular in shape and size. In case of Solid dispersions, it was difficult to distinguish the presence of drug crystals. The drug surface in solid dispersion seems to be more porous in nature. Solid dispersions appeared as uniform and homogeneously mixed mass with wrinkled surface. Drug crystals appeared to be incorporated into the particles of the polymers. The solid dispersion looked like a matrix particle. The results could be attributed to dispersion of the drug in the molten mass of the polymer.

Stability studies

Stability studies of SD9 formulation was performed for drug content and *in vitro* drug release studies for 3 months at accelerated stability conditions as per ICH guidelines. The optimized formulation was stable during 3 months period. From these results it was concluded that the formulation was stable and retained most of its properties with minor differences. The results are summarized in Table 4.

Micromeretic properties of powder blends of fast disintegrating tablets

The micromeretic properties of powder blends are found to be within the IP limits and summarized in Table 6.

Preparation of fast disintegrating tablets of Tenoxicam

Twenty-seven formulations (TF1-TF27) for active layer were prepared by direct compression method (Table 5) using 3^3 Response surface method with superdisintegrants like Gellan Gum, Fenugreek Seed Mucilage and L-HPC, and the prepared tablets were shown in Figure 12.

Physico-chemical properties of Fast Disintegrating Tablets of Tenoxicam

The prepared tablets were evaluated for different physicochemical properties and the results are found to be within the pharmacopoeial limits, which depicted in Table 7.

In vitro drug release profile of fast disintegrating tablets of Tenoxicam was shown in Figure 13, 14, 15 and 16.

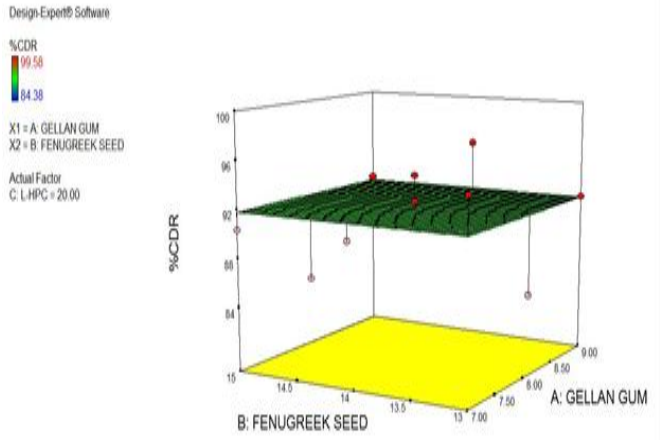


Fig. 17: Response surface plot showing the influence of amount of Superdisintegrants on the release profile of Tenoxicam for % Cumulative Drug Release.

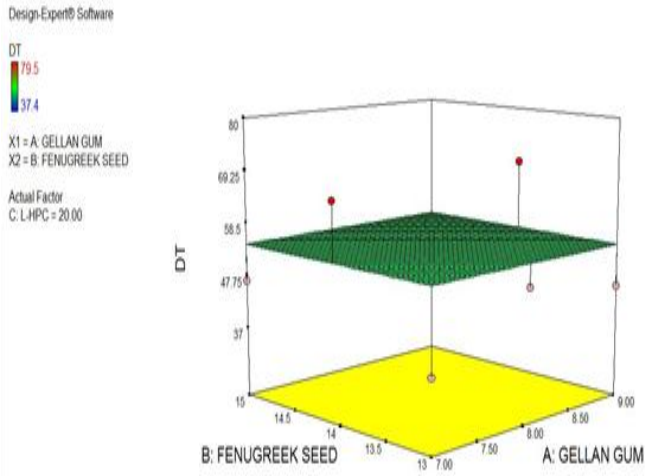


Fig. 18: Response surface plot showing the influence of amount of superdisintegrants on Disintegration Time of Tenoxicam

Design of Experiment

This method is mainly used to explain the effect of one factor on another factor, whether this effect is significant or not, if significant how it influences the response. In this present work the effect of one factor (L-HPC) on other two factors (Gellan Gum, Fenugreek Seed Mucilage) is explained. In the graph (Figure 17) the effect of L-HPC Mucilage on % cumulative drug release is examined and it clearly indicates that there is a very significant effect of L-HPC on % cumulative drug release. From the *in vitro* drug release study observed that as concentration of superdisintegrants increase, % drug release was increased to certain level

beyond it as the concentration of superdisintegrants increase, % drug release was decreased. But prediction of results of % drug release, response surface plot was plotted for graphical representation of results. Figure 18 showed common effect of superdisintegrants concentration. We can conclude from the contour plot for formulation batch TF1 to TF27.

In the graph the effect of L-HPC on disintegration time release is examined and it clearly indicates that there is a very significant effect of L-HPC on Disintegration time. From the disintegration time study observed that as concentration of superdisintegrants increase, disintegration Time was decreased**.**

All the twenty-seven formulations that were prepared and evaluated for various parameters such as compatibility studies, drug content, weight variation, hardness, thickness, friability, disintegration time.

In vitro dissolution studies

All the formulations evaluated for *in vitro* drug release studies. The formulation TF13 showed highest drug release of 99.68 ± 1.22 % at 10 mins where as Marketed product for the same time shows the drug release of 92.77 ± 1.52 %.

Stability Studies

The developed formulation was subjected to stability studies for 6 months according to ICH guidelines to evaluate its stability and the integrity of the dosage form. From these results, it was concluded that, theoptimized formulation is stable and retained their original properties of hardness, disintegration test and *in vitro* dissolution studies with minor differences (Table 8).

From the present investigation the solid dispersions of Tenoxicam prepared with Kollidon CL, PVP K30 and Poloxamer 127, in 1:1:1,1:2:1 and 1:3:1 by using solvent evaporation method was incorporated in the fast disintegrating tablets shown highest drug release. Solid dispersions showed a better dissolution compared to the pure drugs and among all the other formulations SD9 shows high percentage drug release i.e. 99.11 ± 5.17% for 90 min and selected as an optimized formulation for the preparation of fast disintegrating tablets of Tenoxicam. The prepared solid dispersions were analyzed for all the physical parameters, drug: carrier interactions like FTIR, SEM, XRD. Gellan Gum, Fenugreek Seed Mucilage and L-HPC (low, middle and high concentrations) used in the preparation of fast disintegrating tablets prepared by direct compression method using 3^3 Response surface method. The post compression parameters of all the prepared tablets were within the limits. TF13 was selected as optimized formulation based on its highest disintegration time 36 sec and drug release 99.68 ± 1.52% for 10 min. Drug-excipient characterization also revealed that there is no interaction. Hence it concluded that solid dispersions incorporated fast disintegrating tablets is very useful approach for immediate release of Tenoxicam in the efficient management of inflammation and pain.

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