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DEVELOPMENT, CHARACTERIZATION, AND *IN VITRO* EVALUATION OF MOUTH DISSOLVING TABLETS OF TAMOXIFEN

Sarad Pawar Naik Bukke[1*], Tamma Avinash Reddy[2], Narayana Goruntla[3], Hussaini Bello[1]

[1*]Department of Pharmaceutics and Pharmaceutical Technology, Kampala InternationalUniversity, Western Campus, Uganda
[2]Department of Pharmaceutics, Rao's College of Pharmacy, Nellore, Andhra Pradesh, India
[3]Department of Clinical Pharmacy and Pharmacy Practice, Kampala International University, Western Campus, Uganda

***Corresponding Author:**
*Sarad Pawar Naik BUKKE, Department of Pharmaceutics and Pharmaceutical Technology, Kampala International University, Western Campus, P.O. Box 71, Ishaka - Bushenyi, Uganda
drsaradpawar@kiu.ac.ug, +256-760254289

Abstract
The present study was carried out on Tamoxifen by employing solid dispersion technique. The λ_{max} of phosphate buffer pH 6.8 of Tamoxifen were found to be at 276 nm. The pure drug the optimised Solid dispersion formulations were subjected to FTIR studies. The results were showed that there is no interaction between the drug and excipients. The micrometric properties of blend of Tamoxifen soild dispersion were characterized with respect to Angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio**.** Angle of repose was less than 28^0, Carr's index values were 10 to 17 for the pre compression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.2 for all the batches indicating good flow properties. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 2 to 3 kg/cm^2 and the friability values were less than 1% indicating that the tablets were compact and hard. The thickness of the tablets ranged between 3.1 to 3.8 mm. All the formulations satisfied the content of the drug as they contained 96-100% of Tamoxifen and good uniformity in drug content was observed. Thus, all the physical attributes of the prepared tablets were found to be practically within control limits.The dissolution profile of Tamoxifen tablets was compared between solid dispersion tablets. The Tamoxifen solid dispersion tablets showed better release in phosphate buffer pH 6.8, in that F2 showed good drug release i.e., 99.89 at 15 minutes. F2 formulation was taken as optimised formulation.

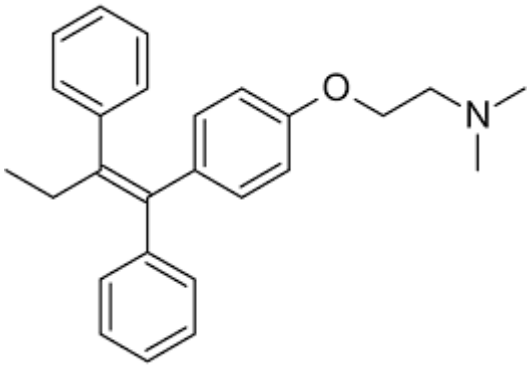
Key Words: Tamoxifen, Solid dispersion tablets, Development, Characterisation

INTRODUCTION
The gold standard in pharmaceutical industry is the oral delivery because it is the easiest, safest, economical and convenient method for the drug delivery.[1] Mouth dissolving tablets have become the most demanding application during last decades and in the pharmaceutical industry this field has become a rapidly area. Mouth dissolving tablets during insertion in the mouth should have to

dissolve or disintegrate in the mouth within 15sec to 3 minutes without the help or need of any drinking agent like water.[2-3] These mouth dissolving tablets can be given anytime, anywhere to anyone who needs this without the presence of water and these will show the effective action in few minutes.[4-5] Methods to improve patient's compliance have always attracted scientists towards the development of fancy oral drug delivery systems.[6] Among them, mouth dissolving drug delivery systems (MDDDS) have acquired an important position in the market by overcoming previously encountered administration problems and contributing to extension of patent life.[7] MDDDS have the unique property of rapidly disintegrating and/or dissolving and releasing the drug as soon as they come in contact with saliva, thus obviating the requirement of water during administration. Therefore, these dosage forms have lured the market for a certain section of the patient population which include dysphagic, bed ridden, psychic, geriatric and paediatric patients.[8] Several techniques have been developed in the recent past, to improve the disintegration quality of these delicate dosage forms without affecting their integrity.[9-10]

Tamoxifen is indicated to treat estrogen receptor positive metastatic breast cancer in adults, as an adjuvant in the treatment of early-stage estrogen receptor positive breast cancer in adults, to reduce the risk of invasive breast cancer after surgery and radiation in adult women with ductal carcinoma in situ. Tamoxifen competitively inhibits estrogen binding to its receptor, which is critical for its activity in breast cancer cells.1 Tamoxifen leads to a decrease in tumor growth factor α and insulin-like growth factor 1, and an increase in sex hormone binding globulin.[11] The increase in sex hormone binding globulin limits the amount of freely available estradiol.[12] These changes reduce levels of factors that stimulate tumor growth. Chemical name (2-{4-[(1Z)-1,2-diphenylbut-1-en-1-yl] phenoxy} ethyl) dimethylamine. Chemical Formula $C_{26}H_{29}NO$. Molecular weight is 371.5. It Very slightly soluble in distilled water and acetonitrile; slightly soluble in ethanol; and freely soluble in methanol. Atorvastatin is rapidly absorbed after oral administration with maximum plasma concentrations achieved in 1 to 2 hours. Figure1 shows structyre of Atorvastatin. Tamoxifen is soluble in chloroform at 50 mg/ml and yields a clear, colorless to faint yellow solution. It is also soluble in methanol, ethanol, 2-propanol and propylene glycol. Stock solutions of tamoxifen can also be prepared in DMSO at 10 mM.

Figure 1: Chemical structure of Tamoxifen



The main aim of the work is to formulate Tamoxifen tablets using solid dispersion method. The main objective of this work is to compare the dissolution rate between formulations prepared by solid dispersion method, to evaluate pre and post compression studies, Drug and Excipient compatibility studies

MATERIALS:

Tamoxifen Procured from CIPLA Pharma**,** Provided by Sura Labs. PEG 4000, Polaxomer, Camphor, Mannitol purchased from Nihar traders pvt Ltd, Magnesium stearate, Talc from S.D. Fine chemical Pvt.Ltd, Mumbai, Explotab, Magnesium stearate from Himedia Laboratories.

METHODOLOGY

Determination of Wavelength

10 mg of pure drug was dissolved in 10 ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10µg/ml). The working solution was taken for determining the wavelength.

Determination of Calibration Curve

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution required concentrations were prepared (shown in Table) and those concentrations absorbance were found out at required wavelength.

Fourier Transform Infrared (FTIR) spectroscopy

The formulations were subjected to FTIR studies to find out the possible interaction between the drug and the excipients during the time of preparation. FT IR analysis of the pure drug and optimised formulation were carried out using an FT IR spectrophotometer (Bruker FT-IR - GERMANY).

Formulation Development

Formulation development for solid dispersion

Solid dispersions were prepared by solvent evaporation method. Methanol was used as solvent. Tamoxifen and Water-soluble polymers such as Polaxomer and PEG 4000 were selected as carriers. Drug and polymers were taken in 1:1 ratio stated in the formulation chart (Table). The prepared solid dispersions were passed through the sieve no 20 to get uniform sized particles. The solid dipersions were mixed with required quantities of super disintegrants, diluent, lubricant and glidant (shown in Table 6.2). The blend was evaluated for precompression parameters.

Table1: Formulation of solid dispersion showing various compositions (Ratios only)

	SD1	SD2	SD3	SD4	SD5
Drug	1	1	1	1	1
Polaxomer	1	2	--	--	1
PEG 4000	--	--	1	2	1

Table 2: Formulation of tablet by using solid dispersion

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Equivalent to 10mg	SD1 (20mg)	SD2 (30mg)	SD3 (20mg)	SD4 (30mg)	SD5 (30mg)	SD1 (20mg)	SD2 (30mg)	SD3 (20mg)	SD4 (30mg)	SD5 (30mg)
Explotab/sodium starch glycolate	15	15	15	15	15	-	-	-	-	-
Crosspovidone	-	-	-	-	-	15	15	15	15	15
Mg.stearate	5	5	5	5	5	5	5	5	5	5
Aerosil	5	5	5	5	5	5	5	5	5	5
Mannitol	55	45	55	45	45	55	45	55	45	45
Total weight	100	100	100	100	100	100	100	100	100	100

Micrometric Properties

Angle of repose: The angle of repose of was determined by fixed funnel method. The accurately weighed physical mixtures were taken in a funnel. The height of the funnel was adjusted to 2cm, the

tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through the funnel into the surface.

Bulk Density: Bulk density measurements were carried by placing a fixed weight of powder in a graduated cylinder, and the volume occupied was measured. The bulk volume (V_b) and weight of the powder were measured.

Tapped density: The measuring cylinder containing weighed mass of powder. The cylinder was then tapped at a constant velocity until a constant volume was obtained. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the powder was measured.

Carr's Index (%): The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of material because all of these influence the compressibility index. The simple method for measurement of free flow of powder is Carr's Index, a sign of the easiness

Hausner Ratio: Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

Evaluation of Tamoxifen tablets:

Weight variation: Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation three batches were calculated. It passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown.

Thickness: The thickness of Tamoxifen tablets was determined by using digital micrometer. Ten individual tablets from each batch were used and the results averaged.

Hardness: The hardness of the tablets was determined by using Monsanto hardness tester. Six individual tablets from each batch were taken and results averaged.

Friability: The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed six tablets were placed in Roche friabilator and rotated at 25 rpm for 4 min. Percentage friability was calculated using the following equation.

Disintegration test: Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets Apparatus was run for 10 minutes and the basket was lift from the fluid and observed for disintegration of tablets.

Content of uniformity: The tablets were individually weighed and crushed. The quantity of powder equivalent to mass of the one tablet was extracted in 10ml of methanol and then made up 100ml with phosphate buffer pH 6.8, shaken for 30mins. The solution was filtered through whattmen filter paper. The drug content was determined by UV spectrometer at respective wavelength for Tamoxifen after suitable dilution with phosphate buffer pH 6.8.

***In vitro* Dissolution Study:**Drug release from formulated Tamoxifen tablets was determined by using USP dissolution test apparatus II (Paddle apparatus). The tablets were place in 900 ml of dissolution medium as phosphate buffer pH 6.8 maintained at 37 ± 0.5 °C and 50 rpm. At appropriate intervals (5, 10, 15, 30, 45 and 60) 5ml of the samples were taken and the dissolution media was then replaced by 5ml of fresh dissolution fluid to maintain a constant volume. After

proper dilution, the samples were then analyzed at respective wavelength by UV-spectrophotometer. The concentration was calculated by using calibration curve.

RESULTS AND DISCUSSION

Analytical Method Development

Construction of calibration curve for Tamoxifen:

The λmax of phosphate buffer pH 6.8 of Tamoxifen were found to be at 276 nm. Standard graphs of Tamoxifen in phosphate buffer pH 6.8 were shown in Table 3. Good linearity was observed with concentration verses absorbance. Its R^2 value in 0.1N HCl and phosphate buffer pH 6.8 was0.999 which were very nearer to '1' and so obeys "Beer -Lambert" law.

Table 3: calibration curve of Tamoxifen in phosphate buffer pH 6.8

Concentration(µg/mL)	Absorbance
0	0
5	0.145
10	0.309
15	0.439
20	0.585
25	0.747

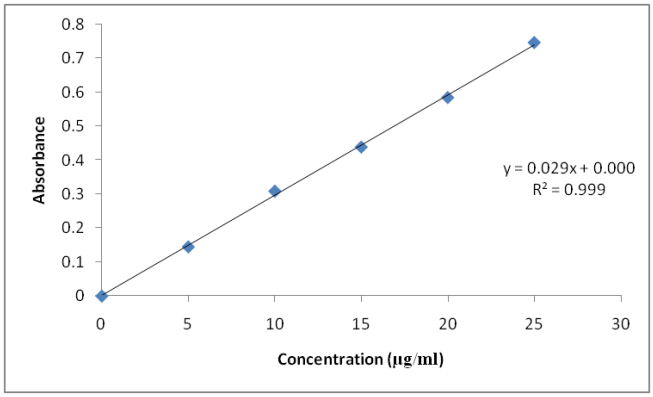


Figure 2: Calibration curve of Tamoxifen in phosphate buffer pH 6.8

Drug Excipient Interactions

Fourier transform infrared (FTIR) spectroscopy studies:

The pure drug and the optimised formulation (F2) were subjected to FTIR studies. The results were showed that there is no interaction between the drug and excipients.

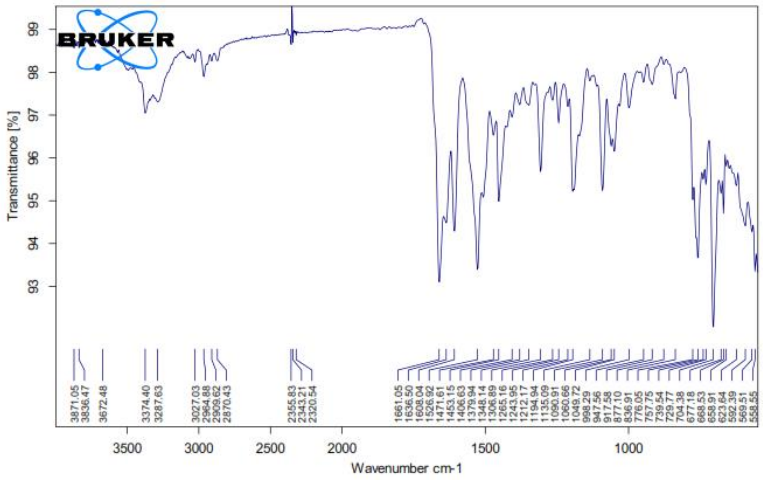


Figure 3: FT-IR Spectrum of Tamoxifen pure drug.

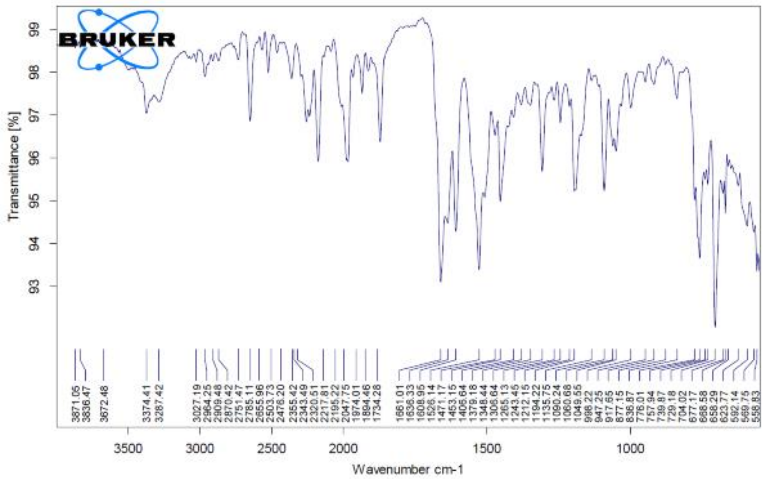


Figure 4: FT-IR Spectrum of Optimised Formulation (F2)

Micromeritic properties

The micrometric properties of blend of Tamoxifen soild dispersion were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio**.** Angle of repose was less than 28^0, Carr's index values were 10 to 17 for the pre compression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.2 for all the batches indicating good flow properties.

Table 4: Evaluation of pre compression parameters of solid dispersion blend Post compression parameters:

Formulation Code	Angle of repose(θ)	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index	Hausner ratio
F1	25.74	0.39	0.48	18.75	1.23
F2	26.03	0.32	0.38	15.78	1.18
F3	25.73	0.35	0.42	16.66	1.20
F4	27.14	0.36	0.43	16.27	1.19
F5	24.63	0.38	0.46	17.39	1.21
F6	24.74	0.32	0.41	12.12	1.25
F7	26.03	0.33	0.41	15.5	1.24
F8	25.73	0.35	0.40	22.2	1.14
F9	26.63	0.35	0.41	13.19	1.17
F10	25.31	0.56	0.62	9.67	1.2

The results of the weight variation, hardness, thickness, friability, and drug content of the solid dispersion tablets were given in Table. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 2 to 3 kg/cm^2 and the friability values were less than 1% indicating that the tablets were compact and hard. The thickness of the tablets ranged between 3.1 to 3.8 mm. All the formulations satisfied the content of the drug as they contained 96-100% of Tamoxifen and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within control limits.

Table 5: Evaluation of post compression parameters of solid dispersion tablets

Formulation code	Average Weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%loss)	Disintegration time (sec)	Content uniformity (%)
F1	98	3.2	2.5	0.39	18	96.31
F2	99	3.1	2.1	0.29	14	98.34
F3	101	3.4	2.7	0.32	17	97.36
F4	99.8	3.6	2.4	0.41	16	96.42
F5	102	3.8	2.6	0.26	18	96.59
F6	101	3.3	2.7	0.28	19	99.33
F7	100	3.5	2.2	0.37	20	99.45
F8	102	3.2	2.3	0.48	22	99.56
F9	101	3.2	2.8	0.54	24	98.96
F10	101	3.4	2.2	0.65	23	98.78

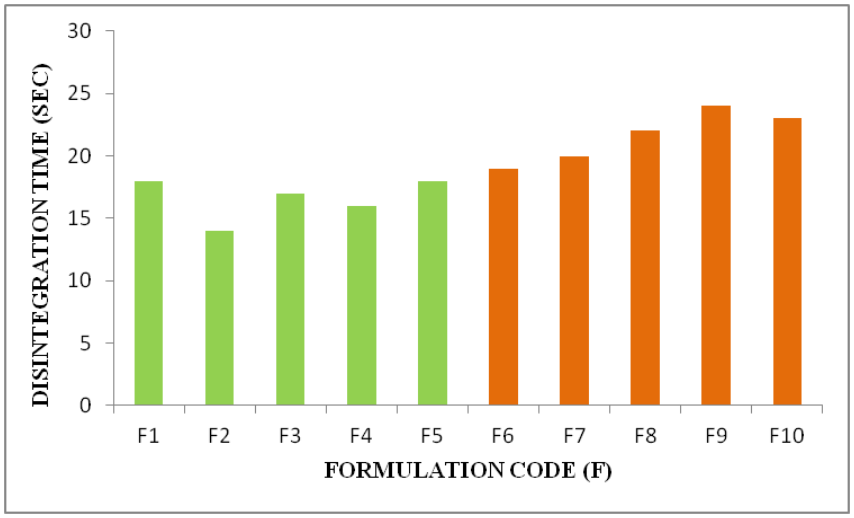


Figure 5: Disintegrations time of formulations

From the above pre and post compression of solid dispersion tablets of all the required evaluation tests were found to be within limit. Less disintegration time is F2 formulation i.e., 14 seconds.

In vitro Dissolution Studies

All the solid dispersion formulations of Tamoxifen were subjected to In vitro dissolution studies, these studies were carried out using phosphate buffer pH 6.8 by using dissolution apparatus type II. The dissolution profile of Tamoxifen tablets were compared between solid dispersion tablets. The Tamoxifen solid dispersion tablets showed better release in phosphate buffer pH 6, in that F2 showed good drug release i.e., 99.89 at 15 minutes.

Table 6: *In vitro* dissolution studies of formulated solid dispersion tablets by using Explotab/sodium starch glycolate as super disintegrant

Time(min)	F1	F2	F3	F4	F5
0	0	0	0	0	0
5	29.86	36.33	21.5	30.48	31.06
10	42.72	62.18	56.8	53.61	59.88
15	68.75	99.89	58.75	69.83	79.52
20	80.35		70.35	82.41	95.64
30	87.94		77.94	96.54	
45	96.24		89.5		
60	96.24		91.3		

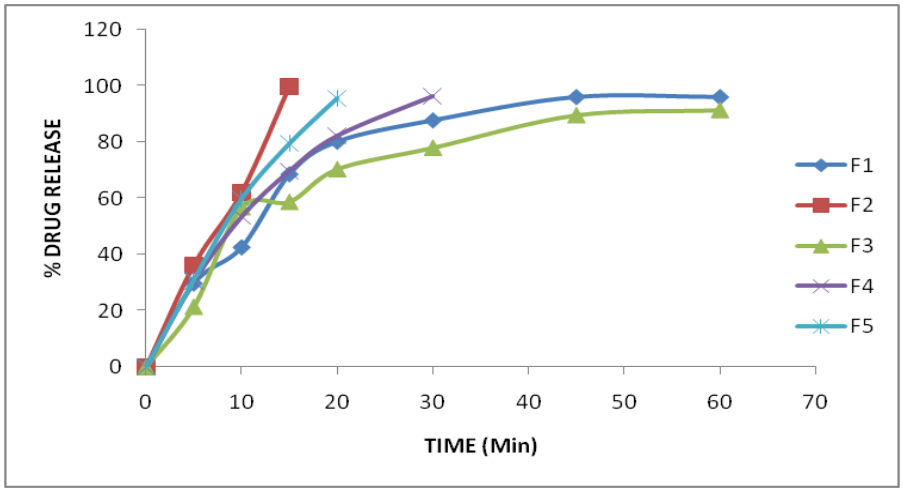


Figure 6: *In vitro* dissolution studies of formulated solid dispersion tablets by using Explotab/sodium starch glycolate as super disintegrant

Table 7: *In vitro* dissolution studies of formulated solid dispersion tablets by using Crosspovidone as super disintegrant

Time(min)	F6	F7	F8	F9	F10
0	0	0	0	0	0
5	32.86	44.33	21.5	30.47	28.96
10	54.56	59.89	32.8	38.48	39.16
15	69.75	88.2	49.75	52.68	58.97
20	73.34	97.2	52.32	69.46	78.65
30	81.94		58.94	82.17	87.53
45	96.5		63.28	96.58	
60	96.5		88.14	96.58	

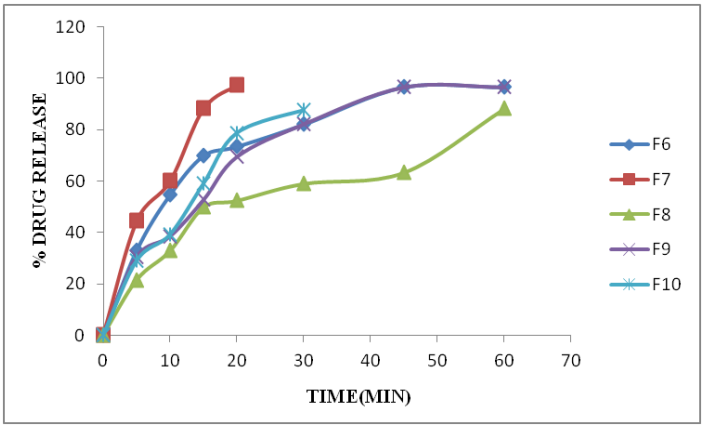


Figure 7: *In vitro* dissolution studies of formulated solid dispersion tablets by using Crosspovidone as super disintegrant

From the above graphs it was revealed that F2 formulation was optimised formulation. Why because in that F2 showed good drug release i.e., 99.89% at 15 minutes and less disintegration time is F2 formulation i.e., 14 seconds. Hence F2 formulation considered as optimised formulation.

CONCLUSION

The present study was carried out on Tamoxifen by employing solid dispersion technique. The λ_{max} of phosphate buffer pH 6.8 of Tamoxifen were found to be at 276 nm. Standard graph of Tamoxifen in phosphate buffer pH 6.8 was plotted. Good linearity was observed with concentration verses absorbance. Its R^2 value in phosphate buffer pH 6.8 was 0.999 which were very nearer to '1' and so

obeys “Beer -Lambert” law. The pure drug the optimized Solid dispersion formulations were subjected to FTIR studies. The results were showed that there is no interaction between the drug and excipients. The micrometric properties of blend of Tamoxifen soild dispersion were characterized with respect to angle of repose, bulk density, tapped density, Carr’s index and Hausner’s ratio**.** Angle of repose was less than 28^0, Carr’s index values were 10 to 17 for the pre compression blend of all the batches indicating good to fair flowability and compressibility. Hausner’s ratio was less than 1.2 for all the batches indicating good flow properties. The results of the weight variation, hardness, thickness, friability, and drug content of the solid dispersion tablets were given in Table. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 2 to 3 kg/cm^2 and the friability values were less than 1% indicating that the tablets were compact and hard. The thickness of the tablets ranged between 3.1 to 3.8 mm. All the formulations satisfied the content of the drug as they contained 96-100% of Tamoxifen and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within control limits. All the solid dispersion formulations of Tamoxifen were subjected to *in vitro* dissolution studies, these studies were carried out using phosphate buffer pH 6.8 by using dissolution apparatus type II. The dissolution profile of Tamoxifen tablets were compared between solid dispersion tablets. The Tamoxifen solid dispersion tablets showed better release in phosphate buffer pH 6.8, in that F2 showed good drug release i.e., 99.89 at 15 minutes. F2 formulation was taken as optimised formulation.

Declarations

Ethicsapproval

Not applicable

Consent to Participate

Not applicable

Consent to Publication

All the authors have read and agreed to the final copy of the finding as contained in the manuscript.

Availability of data and materials

The datasets/information used for this study are available on reasonable request.

Conflicting interest

All authors report that there was no conflict of interest in this work.

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Author Contributions

Conceptualisation: Sarad Pawar Naik Bukke, Methodology and investigation: Tamma Avinash Reddy Analysis, interpreted the data and writing—original draft preparation: Narayana Goruntla, HussainiBello Writing—review and editing: Sarad Pawar Naik Bukke, Tamma Avinash Reddy, Narayana Goruntla, HussainiBello.

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