DESIGN, DEVELOPMENT AND EVALUATION OF ORAL DISSOLVING FILM OF TIZANIDINE

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Abstract: This study focuses on the design, development, and evaluation of an oral dissolving film (ODF) containing Tizanidine, a centrally acting muscle relaxant. The aim was to enhance patient compliance by providing a fast-dissolving, convenient dosage form. The ODF was formulated using hydroxypropyl methylcellulose (HPMC) as the film-forming polymer, glycerine as a plasticizer, and appropriate sweeteners and flavors to improve palatability. The films were evaluated for their physicochemical properties, drug release profile, and stability. The results indicated that the optimized ODF formulation provided rapid drug release, satisfactory mechanical properties, and good stability, making it a viable alternative to conventional oral dosage forms.
Keywords: Tizanidine, Oral Dissolving Film, HPMC, Drug Release, Patient Compliance.

1: Introduction

Oral dissolving films (ODFs) represent an innovative and patient-friendly drug delivery system designed to improve the convenience and compliance of medication administration, particularly for populations with swallowing difficulties, such as pediatric and geriatric patients. Tizanidine is a muscle relaxant used to manage spasticity; however, its conventional oral dosage forms may pose challenges in terms of rapid onset of action and ease of administration. This study aims to develop an ODF for Tizanidine, optimizing its formulation for fast dissolution and immediate therapeutic effect.

Tizanidine is a centrally acting α2-adrenergic agonist primarily prescribed for the management of spasticity. Its effectiveness in reducing muscle spasticity and improving muscle tone has made it a valuable therapeutic option for patients with neurological disorders such as multiple sclerosis, spinal cord injury, and amyotrophic lateral sclerosis. First approved by the FDA in 1996, tizanidine has since been extensively studied for its pharmacological properties and clinical applications.

Pharmacodynamics and Mechanism of Action

Tizanidine functions by stimulating α2-adrenergic receptors in the central nervous system, which leads to inhibition of excitatory neurotransmitter release. This action primarily occurs at the level of the spinal cord, resulting in decreased motor neuron activity and muscle spasticity. Unlike other muscle relaxants, tizanidine's primary site of action is presynaptic inhibition of motor neurons, providing a targeted approach to managing spasticity without significantly affecting muscle strength.

Pharmacokinetics

Upon oral administration, tizanidine is rapidly absorbed, with peak plasma concentrations reached within 1 to 2 hours. It undergoes extensive hepatic metabolism, primarily via the cytochrome P450 1A2 enzyme, and has a relatively short half-life of approximately 2.5 hours. Due to its hepatic metabolism, caution is advised in patients with liver impairment, and potential drug interactions should be carefully managed, particularly with drugs that inhibit or induce CYP1A2.

Material and Methods

Preparation of calibration curve of Tizanidine: Tizanidine's normal stock solution was created by dissolving 100 mg of the medication in the bare minimum of distilled water, and then adding SGF to make up the remaining volume. By diluting the primary stock solution ten times, a secondary stock solution with a concentration of 100µg/ml was created from the

standard stock solution. Aliquots ranging from 0.5 ml to 2.5 ml were transferred from this secondary stock solution into a succession of 10 ml volumetric flasks. The final volume was then made up with buffer to give the concentration ranging from 5µg/ml to 25µg/ml. At 320 nm, the absorbance of these solutions was measured in a UV Visible spectrophotometer using SGF as a blank. Three determinations were averaged.

Method of Preparation for Oral Dissolving Film

Calculation of Oral dissolving film

Diameter of Petri dish: (Dose of tizanidine as per record 8mg)

Radius of the petri dish = 6 cm Diameter = Radius/2 = 6/2 =3 cm. πr2 = 3.14 x 3 x 3 = 28.26 cm2

Now, Dose is % mg and cut the pieces in 2 cm x 2 cm = 4 cm2 4 cm2 contain 5 mg of drug.

So, 28.26 cm2 contains = 28.26/4 = 7.06 and 7.06 x 5 = 35.32 mg drug So 2 ml contain 35.32 mg drug

Then, 10 ml contain drug = 176.60 mg drug

Method of preparation of (placebo)

For the film preparation, the solvent casting method was utilised. Weighed the polymer precisely and submerged it in 10 millilitres of water. Aspartame and the specified amount of citric acid were added to this mixture, and it was agitated for 45 minutes. Stir the solution continuously while adding the polymer solution after it has been well combined. PEG 400 plasticizer was finally added, stirring constantly. After 45 minutes of vigorously stirring the final dispersion, the solution was sonicated for 15 minutes to eliminate any remaining air bubbles. The dispersion was then placed aside for an hour to allow the foams to subside. Glycerol was used to lubricate the petri dish in the interim to reduce the possibility of film damage during removal. After transferring two millilitres of the final dispersion into the measuring cylinder, the solution was poured into a 28.26 cm2 clean, dry petri plate. After that, the films were dried for one to two hours at 40°C in a vacuum tray dryer. After that, the films were taken out and chopped to a size of (2x2) cm2. After that, these films were kept in appropriate packaging at room temperature.

Table 1: Formulation of Oral Dissolving Films (Placebo)

INGREDIENTS	PF1	PF2	PF3	PF4	PF5	PF6	PF7	PF8	PF9	PF10
Sodium Alginate (gm)	0.9	1.2	--	--	--	--	--	--	--	--
Eudragit (gm)	--	--	0.9	1.2	--	--	--	--	--	--
Pullulan (gm)	--	--	--	--	0.9	1.2	--	--	--	--
Sod. Starch Glycolate (gm)	--	--	--	--	--	--	0.9	1.2	--	--
HPMC (gm)	--	--	--	--	--	--	--	--	0.9	1.2
PEG-400 (ml)	1	1	1	1	1	1	1	1	1	1
Citric Acid (mg)	200	200	200	200	200	200	200	200	200	200
Aspartame (mg)	10	10	10	10	10	10	10	10	10	10
Colouring Agent	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*
Flavouring Agent	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*
Water (ml)	10	10	10	10	10	10	10	10	10	10

Table 2: Trials Taken To Study the Effect of Various Concentration of PEG400 on Parameters of Oral Dissolving Film

INGREDIENTS	TF1	TF2	TF3	TF4	TF5	TF6	TF7	TF8	TF9	TF10
Pullulan (gm)	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
PEG-400 (ml)	--	0.2	0.4	0.8	1	1.2	1.4	1.6	1.8	2
Citric Acid (mg)	200	200	200	200	200	200	200	200	200	200
Aspartame (mg)	10	10	10	10	10	10	10	10	10	10
Colouring Agent	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
Flavouring Agent	QS	QS	QS	QS	QS	QS	QS	QS	QS	QS
Water (ml)	10	10	10	10	10	10	10	10	10	10

Method of preparation of (Drug Incorporated)

Weighed the polymer precisely and submerged it in 10 millilitres of water. Ten millilitres of water were used to dissolve the necessary amount of

tizanidine. Stirred this solution for 45 minutes after adding the specified amount of aspartame and citric acid. Stir the solution continuously while adding the polymer solution after it has been well combined. PEG 400 plasticizer was finally added, stirring constantly. After 45 minutes of stirring the final dispersion, the solution was sonicated for 15 minutes to eliminate any remaining air bubbles. After that, the dispersion was placed aside for an hour to allow the foams to subside. Glycerol was used to lubricate the petri dish in the interim to reduce the possibility of film damage during removal. After transferring two millilitres of the final dispersion into the measuring cylinder, the solution was poured into a 28.26 cm2 clean, dry petri plate. After that, the films were dried for one to two hours at 40°C in a vacuum tray dryer. After that, the films were taken out and sliced into 2 x 2 cm2 pieces with 5 mg of tizanidine within. After that, these films were kept in appropriate packaging at room temperature.

Table 3: Formulation of Oral Dissolving Films (Drug Incorporated)

INGREDIENTS	PF1	PF2	PF3	PF4	PF5	PF6	PF7	PF8	PF9	PF10
Tizanidine (Mg)	140	140	140	140	140	140	140	140	140	140
Sodium Alginate (gm)	0.9	1.2	--	--	--	--	--	--	--	--
Eudragit (gm)	--	--	0.9	1.2	--	--	--	--	--	--
Pullulan (gm)	--	--	--	--	0.9	1.2	--	--	--	--
Sod. Starch Glycolate (gm)	--	--	--	--	--	--	0.9	1.2	--	--
HPMC (gm)	--	--	--	--	--	--	--	--	0.9	1.2
PEG-400 (ml)	1	1	1	1	1	1	1	1	1	1
Citric Acid (mg)	200	200	200	200	200	200	200	200	200	200
Aspartame (mg)	10	10	10	10	10	10	10	10	10	10
Colouring Agent	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*
Flavouring Agent	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*	q.s*
Water (ml)	10	10	10	10	10	10	10	10	10	10

Result and Discussion:

Chemical Compatibility:

Compatibility study of pure drug Tizanidine with other excipients were carried out prior to the formulation of films. IR spectra of pure drug and DSC of physical mixture of drug-excipients were obtained, which are depictedbelow. All the characteristics peaks of Tizanidine were present in spectra at respective wavelengths. Thus, it shows compatibility between drug and excipients. There was no significant change in the chemical integrity of the drug.

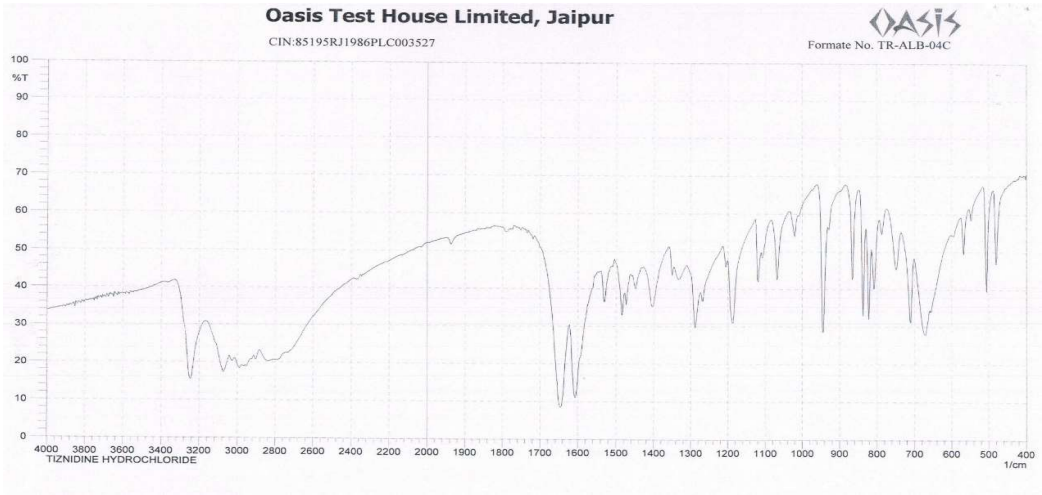

Figure 1: FTIR Spectrum of Tizanidine

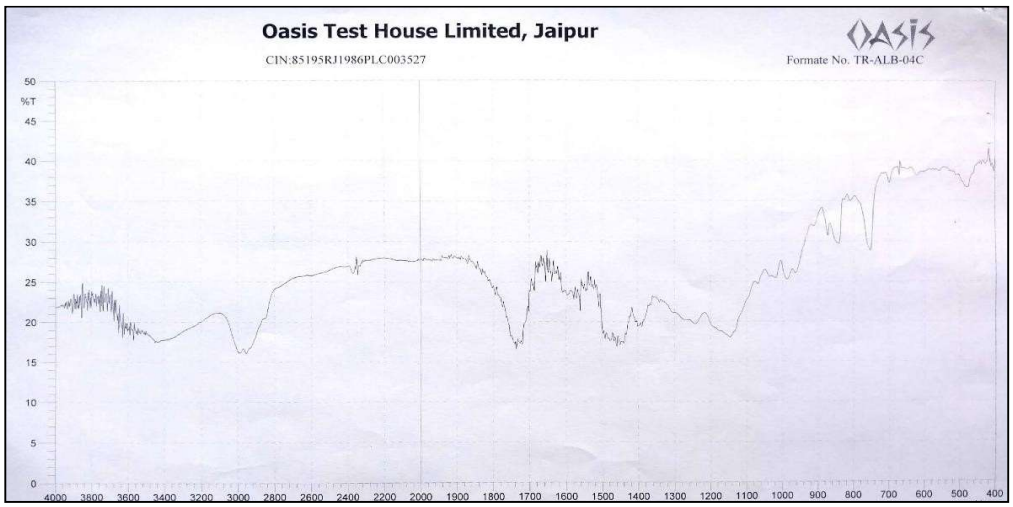

Figure 2: FTIR Spectrum of Tizanidine+Sodium starch glycolate

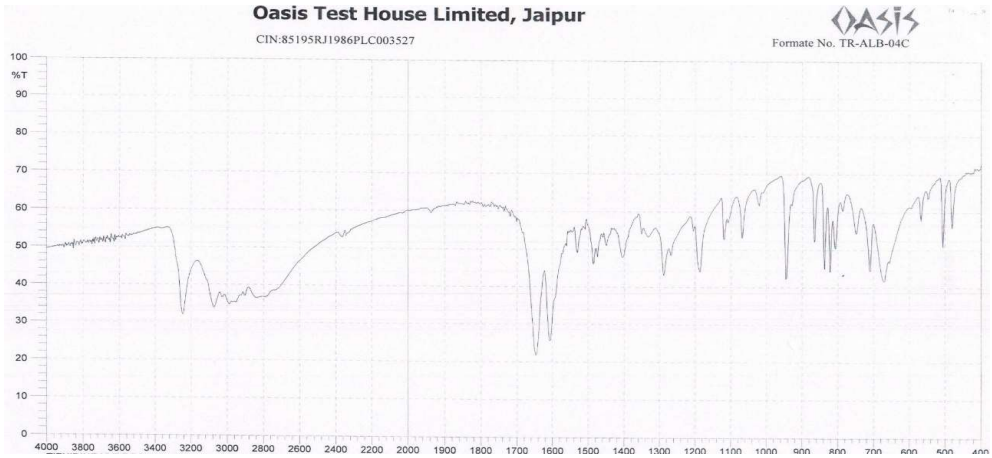

Figure 3: FTIR Spectrum of Tizanidine+Eudragit

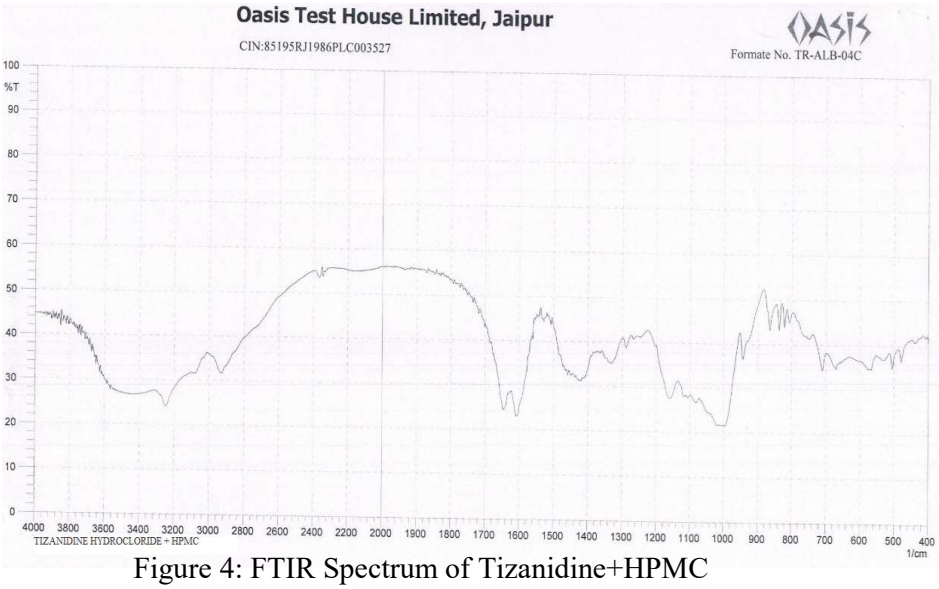

Figure 4: FTIR Spectrum of Tizanidine+HPMC

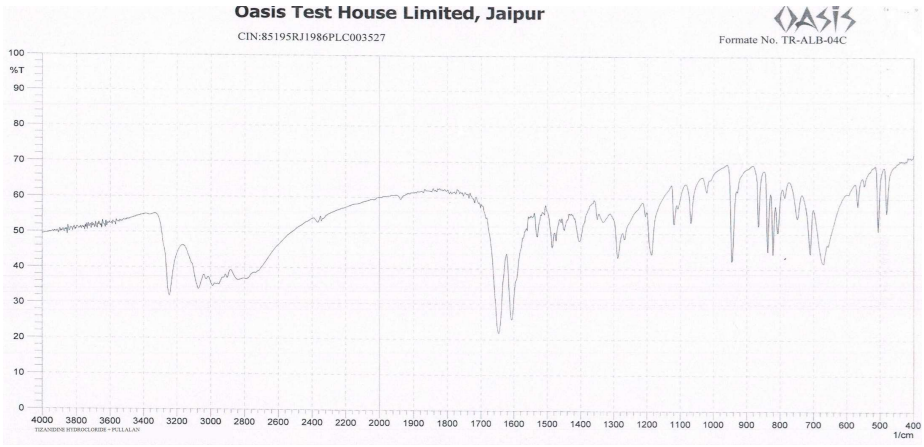

Figure 5: FTIR Spectrum of Tizanidine+Pullalan

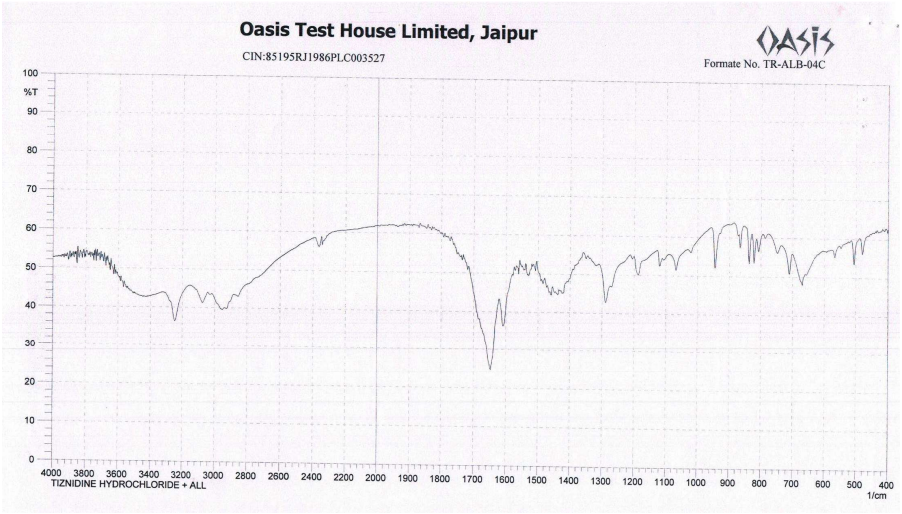

Figure 5: FTIR Spectrum of Tizanidine+All polymers excipients

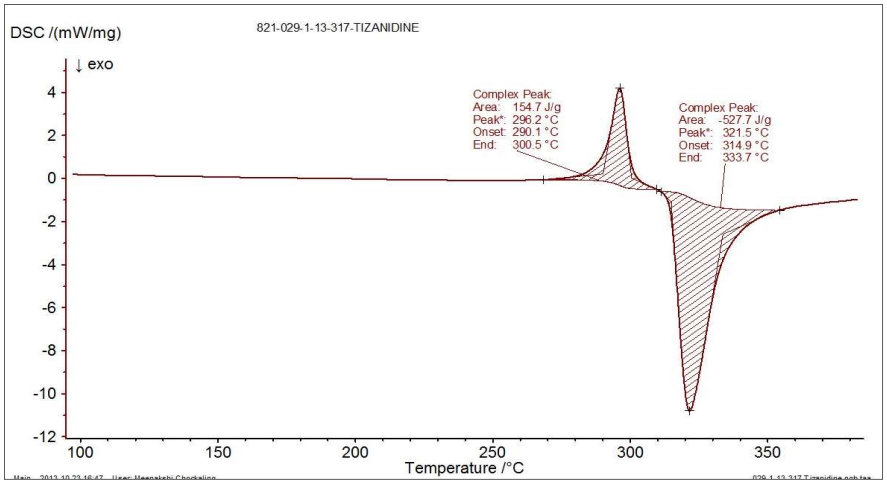

Figure 6: DSC of Tizanidine

Evaluation of Placebo Oral Dissolving Films

Table: 4 Physical Characterization of Oral Dissolving Film

PARAMETERS	FORMULATION CODE									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Weight variation	18.00 ±0.12	21.02 ±0.13	21.14 ±0.17	22.51 ±0.07	20.95 ±0.01	19.70 ±0.12	22.15 ±0.01	19.45 ±0.652	20.68 ±0.05	24.00 ±0.05
Thickness (mm)	0.035 ±0.020	0.038 ±0.013	0.036 ±0.011	0.038 ±0.012	0.037 ±0.011	0.036 ±0.012	0.037 ±0.015	0.038 ±0.012	0.036 ±0.019	0.040 ±0.012
Surface pH	5.00	6.15	6.23	5.87	6.65	5.89	5.18	6.35	7.00	6.44
Folding endurance	200	218	240	265	260	238	239	249	256	270

Appearance: Films containing eudragit and sodium alginate appeared opaque, while formulations containing drugs with a lower pullulan concentration were transparent and those with a greater pullulan concentration were translucent. Although the HPMC films were transparent as well, the pullulan-containing films had a nice feel and texture.

Weight of film: Using an electronic balance, 4 cm2 of films were weighed, and the average weight was determined. The films weigh between 18 to 24 mg.

Thickness of film: Three films were chosen at random, and their thicknesses were measured with a standard Vernier calliper. The films were between 0.035 and 0.040 mm thick.

Surface pH of film: To look into the potential for any in vivo adverse effects, the film's surface pH was measured. It was decided to maintain the surface pH as near to neutral as feasible because an acidic or alkaline pH could irritate the buccal mucosa. Films have pH values ranging from 5 to 7.

Folding endurance: Folding endurance was determined by repeatedly folding the film at same possible position until it breaks. The folding endurance of films range from 200-270.

Evaluation of Tizanidine Oral Dissolving Films

Table 5: Physical Characterization of Oral Dissolving Film

PARAMETERS	FORMULATION CODE									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Weight variation	19.37 ±0.452	22.07 ±0.323	20.64 ±0.337	21.50 ±0.547	23.69 ±0.601	17.71 ±0.432	22.75 ±0.231	18.75 ±0.652	20.68 ±0.125	22.83 ±0.385
Thickness (mm)	0.040 ±0.010	0.048 ±0.012	0.037 ±0.081	0.053 ±0.090	0.048 ±0.001	0.050 ±0.042	0.047 ±0.065	0.051 ±0.032	0.053 ±0.089	0.036 ±0.042
Surface pH	6.67	6.95	6.43	6.87	6.98	6.89	6.58	6.98	6.87	6.74
Folding endurance	209	219	230	238	260	218	232	246	257	269
Tensile Strength	0.735 ±0.12	0.846 ±0.04	0.985 ±0.09	2.124 ±0.11	2.243 ±0.18	2.345 ±0.04	1.521 ±0.01	1.582 ±0.02	1.624 ±0.11	1.876 ±0.06
Percent Elongation (%)	2.51	2.45	2.48	2.41	2.55	2.38	2.34	2.28	2.32	2.38
Disintegration time	29 ±0.58	23 ±0.15	17 ±0.56	25 ±0.65	8 ±0.12	37 ±0.18	40 ±0.85	30 ±0.45	27 ±0.89	33 ±0.56
Drug content	96.47 ±0.45	98.53 ±0.89	97.32 ±0.41	96.58 ±0.67	99.87 ±0.85	98.87 ±0.78	98.47 ±0.23	96.23 ±0.68	97.30 ±0.44	97.83 ±0.49

Organoleptic and physical Evaluation: Formulations containing drug with lower concentration of pullulan were transparent, higher concentration of pullulan were translucent and films containing eudragit and sodium alginate were opaque in appearance. HPMC films were also transparent but the films containing pullulan had good texture and feel.

Weight of film: Films of area 4 cm^2 were weighed using electronic balance and the average weight was calculated. The weight of films range from 17.71-23.69 mg.

Thickness of film: The thickness of three randomly selected films was determined using a standard Vernier caliper. The thickness of films were range from 0.036- 0.053 mm.

Surface pH of film: The surface pH of the film was determined in order to investigate the possibility of any side effect in vivo. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH asclose to the neutral as possible. The pH of films range from 6.43-6.98.

Folding endurance: Folding endurance was determined by repeatedly folding the film at same possible position until it breaks. The folding endurance of films range from 209-269.

Tensile Strength: Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. Tensile strength of given formulation is 0.735 to 2.345gm/mm^2

Percent Elongation: For oral dissolving films, the percent elongation typically ranges from 2.28% to 2.55%. This range reflects a balance between sufficient flexibility to avoid tearing during use and adequate mechanical strength to maintain integrity during handling.

Disintegration Time: 2 ml of distilled water was placed in petridish and one film was added on the surface of the water and the time measured until the film was dissolved completely. The disintegration time range from 8-40 seconds.

Drug Assay/ Drug Content: A sample of size 2x2 cm^2 which were placed in the beaker containing 100 ml of distilled water. Dilute 10 ml of this solution to 10 ml with distilled water. Than Absorbance of standard preparation and test preparation was taken using UV double beam spectrophotometer. The drug content of films was found to be between 96.23-99.87%.

In-vitro drug release: The in-vitro dissolution study was carried out in simulated saliva solution pH 6.8 phosphate buffer using USP basket apparatus at 37±0.5°C. Samples were withdrawn at regular time intervals and analysed by UV-Visible spectrophotometer. By this method cumulative drug release and cumulative percentage of drug retained were calculated. The study was carried out at 37°C with stirring speed of 75 rpm in 900 ml of pH 6.8 phosphate buffer dissolution medium. 5 ml of samples were withdrawn at predetermined time intervals of 2,4,6,8 and 10 minutes and replaced with the same volume of buffer. The samples were collected and the absorbance was determined at 320 nm UV-Visible spectrophotometer.

The results of in-vitro release data obtained for all formulations were fitted in two popular models of data treatments as follows:

i Zero-order kinetic model (cumulative percent drug released vs time)

ii First-order kinetic model (log cumulative percent drug remaining vs time)

Table 6.Dissolution Parameters for Formulations

S. No	Formulation code	t25% (min)	t50% (min)	t70% (min)	t90% (min)	Cumulative % drug release in 10 minutes
1.	F1	2.47	5.47	8.13	>10	82.94
2.	F2	2.74	6.10	8.46	>10	87.36
3.	F3	2.00	4.00	6.00	>9	97.21
4.	F4	1.35	3.00	4.22	>8	97.52
5.	F5	1.00	2.00	2.10	>6	98.57
6.	F6	2.98	6.00	8.23	>10	79.87
7.	F7	3.00	5.47	8.12	>10	82.48
8.	F8	2.13	4.47	7.10	>10	89.36
9.	F9	2.00	4.00	6.01	>10	95.58
10.	F10	1.48	2.49	4.47	>10	98.01

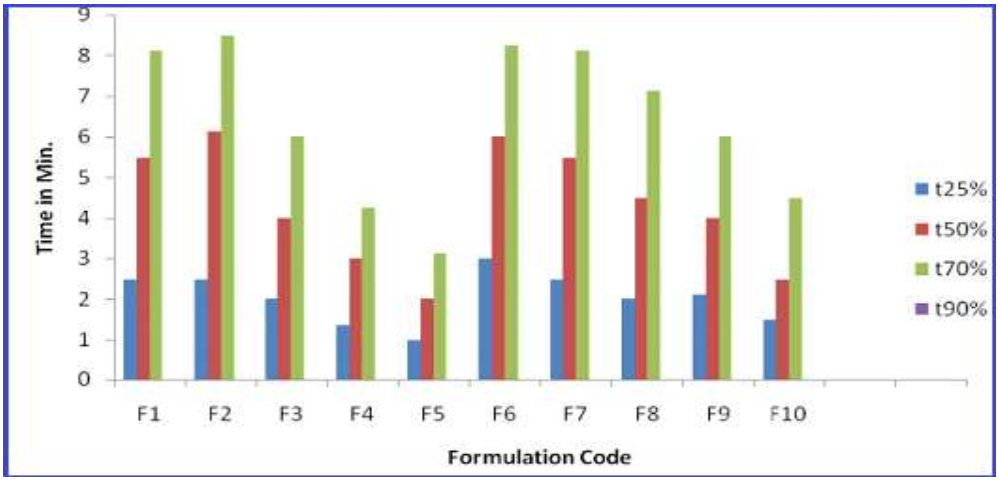

Figure 7: Comparison of Dissolution Parameters (T25%, T50%, T70%, T90%) of oral Dissolving Films of Tizanidine

Assay of Content Uniformity: The result of assay and content uniformity of all batches is shown in table. Content uniformity and assay complies in all batches as all batches are within the specified limit of 95% to 105% as per USP. The formulation F5 shows maximum drug content which is 99.87%.

Study of effects of various ingredients used in Tizanidine oral dissolving film

The study of the effects of various ingredients used in Tizanidine oral dissolving films (ODFs) is crucial for optimizing their formulation, stability, and effectiveness. The optimization of Tizanidine ODFs involves balancing these ingredients to achieve desired mechanical properties, rapid disintegration, acceptable taste, and effective drug delivery.

Data treatment: The in vitro release data were plotted for various kinetic models. To find out mechanism of drug release from all the formulations of Tizanidine mouth dissolving films, the data were fitted according to zero order and first order pattern as illustrated in table. The correlation coefficient (R^2) values of all formulations showed that the formulations follow first order release pattern, as indicated by their high regression coefficient. The R^2 value of zero order was found to be very low i.e 0.457 while that for first order was found to be 0.832 which indicates that the release from formulation F5 was found to be nearly first order release, governed by dissolution through polymer. As per the observations the release of drug also depends upon polymer viscosity. High molecular weight polymer retards release of drug from formulation. Polymers with high molecular weight affect as less the release of the drug from polymer complex.

Table 7: Kinetic Value Obtained From In Vitro Release

Formulation Code	Zero order		First order	
	Ko (mg/h)	R^2	K1 (hr^{-1})	R^2
F1	7.497	0.567	0.487	0.957
F2	7.537	0.482	0.489	0.977
F3	7.597	0.457	0.487	0.969
F4	7.447	0.460	0.402	0.970
F5	8.517	0.628	0.478	0.995
F6	8.123	0.541	0.458	0.832
F7	7.737	0.529	0.263	0.991
F8	6.487	0.466	0.289	0.943
F9	7.861	0.601	0.378	0.907
F10	8.154	0.643	0.432	0.898

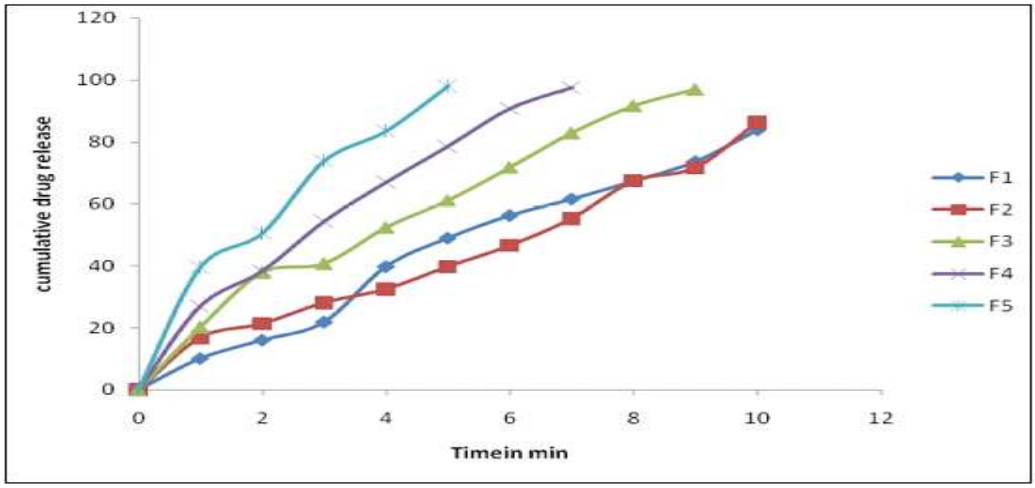

Figure 10: Cumulative Percent Drug Released Vs Time Plots (Zero Order) OfFormulations F1, F2, F3, F4 and F5 in pH 6.8 Phosphate Buffer

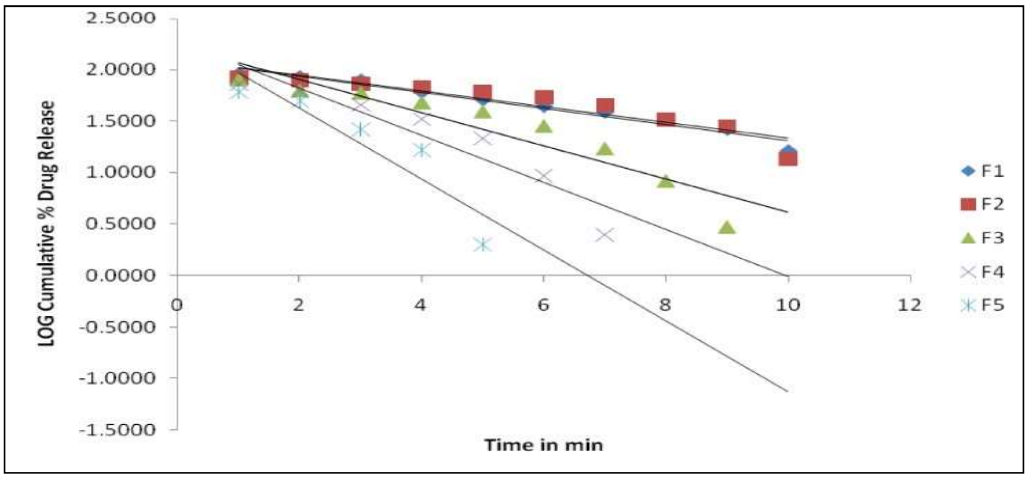

Figure 11: Log Cumulative Drug Remaining Vs Time Plots (First Order) OfFormulations F1, F2, F3, F4 and F5 in pH 6.8 Phosphate Buffer

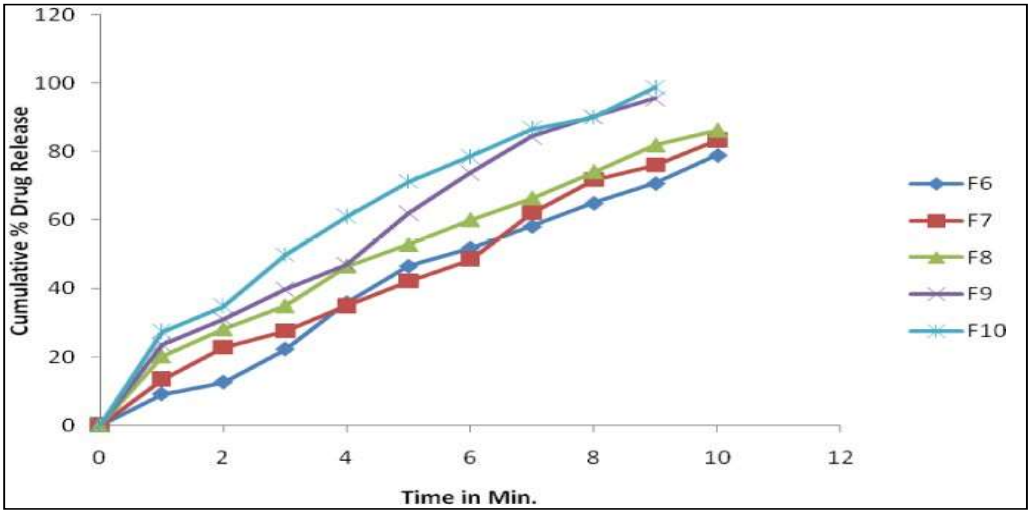

Figure 12: Cumulative Percent Drug Released Vs Time Plots (Zero Order) OfFormulations F6, F7, F8, F9 and F10 in pH 6.8 Phosphate Buffer

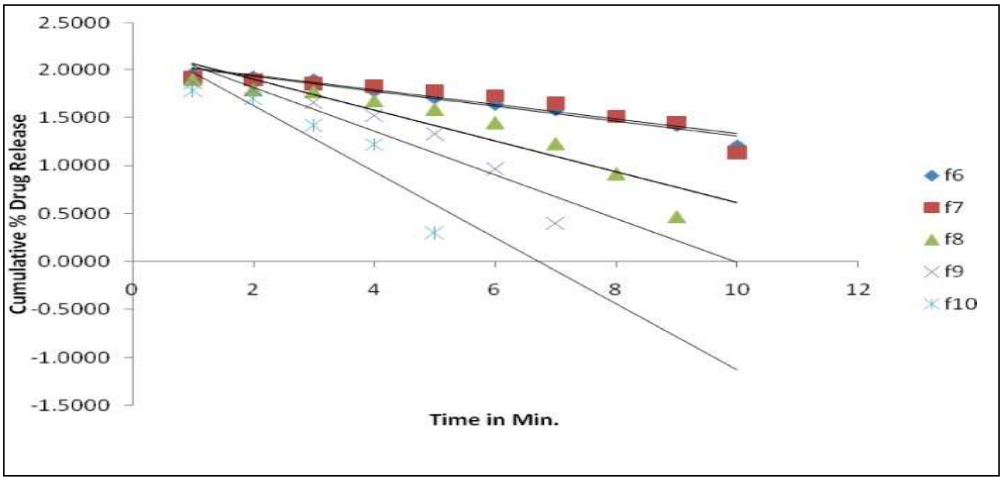

Figure 13: Log Cumulative Drug Remaining Vs Time Plots (First Order) OfFormulations F6, F7, F8, F9 and F10 in pH 6.8 Phosphate Buffer

Stability Studies: Stability studies for the formulation F5 Stability study for the best formulation was done as per the procedure. The ODF was both physically and chemically stable at 4-5^{0}c, Room temperature and 37±5^{0}c. The results were tabulated in Table 8

Table 8: Physical Stability of formulation F5

Parameters	Appearance	pH	Tensile Strength	Percent Elongation (%)	Folding Endurance
Room Temperature	White Smooth	6.98	2.243	2.55	260
37±5^{0}C	No Changes	6.98	No Changes	No Changes	No Changes
4-5^{0}C	No Changes	6.98	No Changes	No Changes	No Changes

Chemical evaluation: The drug content of the formulation was estimated over a period of 3 months. The results were tabulated as follows.

Table 9: Drug content of formulation F5

Storage condition	Withdrawal period (monthly)			
	0	1	2	3
4-5^{0}C	99.87	98.45	97.80	96.90
Room Temperature	99.87	98.40	97.90	97.55
37±5^{0}C	99.87	98.35	97.85	96.80

Conclusion

The current investigation included the formulation, preparation, and evaluation of a oral dissolving film of tizanidine for all of the criteria considered. After being inserted into the oral cavity, the film that has been produced has the ability to disintegrate quickly. Because of its compactness, simplicity of production, and self-administration capabilities. This is due to the fact that it is the most convenient. On the other hand, patients of any age, including children and the elderly, have trouble swallowing traditional medications, which results in poor patient compliance. The revolutionary medication delivery technique that we have created is referred to as "Oral dissolving film." This was done in order to overcome this shortcoming. A revolutionary form of film that dissolves in saliva is being introduced here. The benefits include the ability to administer the medication without the need of water, at any time and in any location. These films are widely used as a dosage form for the treatment of muscular spasms and tone because of the benefits they provide in terms of patient compliance, quick beginning of action.

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