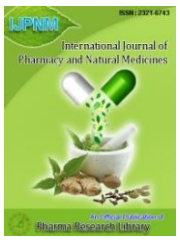

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Design and Development of Liquid Solid System of Poorly Soluble Drug (Class-II) to Improve Dissolution Rate

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A B S T R A C T

The present study aimed to perform a comparative evaluation of natural polymers, namely Xanthan gum and Tragacanth, and to investigate the influence of the physico-chemical properties of the active ingredient on drug release behavior using the liquid-solid compact technique with PEG 400 and Tween 80 as non-volatile vehicles. Pre-compression parameters such as angle of repose, compressibility index, and sieve analysis indicated that the prepared formulations were suitable for the liquid-solid compact method. Tizanidine was successfully formulated into a sustained-release drug delivery system, demonstrating prolonged therapeutic action without reaching toxic plasma concentrations commonly associated with conventional dosage forms. This approach offers the potential to reduce dosing frequency and improve patient compliance. Drug release studies confirmed that the release followed first-order kinetics with the mechanism best fitting the Higuchi model. The findings of the *in vitro* release studies suggest that the developed sustained-release formulation is a promising candidate for further *in vivo* evaluations.

Keywords: Tizanidine, PEG 400, Tragacanth, Xanthan, Tween 80

A R T I C L E I N F O

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1. Introduction

It is well established that the active ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the G.I.T. The poor dissolution of water insoluble drugs is a substantial problem confronting the pharmaceutical industry. The absorption rate of a poorly water-soluble drug, formulated as an orally administered solid dosage form, is controlled by its dissolution rate in the fluid at the absorption site. The dissolution rate is often the rate-determining step in drug absorption.[1] Therefore, the solubility and dissolution behavior of a drug are the key determinants of the oral bioavailability.

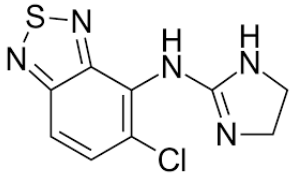

Fig.1: Tizanidine

- **IUPAC Name:** 5-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-2,1,3-benzothiadiazol-4-amine
- **Molecular Formula:** $C_9H_8ClN_5S$

- **Molecular Weight:** 253.71 g/mol
- **Melting Point:** ~280–282 °C (decomposes)
- **pKa:** ~7.4 (imidazoline group)
- **Category:** Centrally acting muscle relaxant; α2-adrenergic receptor agonist
- **Solubility:** Slightly soluble in water; freely soluble in methanol and ethanol

Description

Tizanidine is a centrally acting skeletal muscle relaxant structurally related to clonidine. It works by modulating motor neurons in the central nervous system and is primarily used for the management of spasticity associated with multiple sclerosis, spinal cord injury, and other neurological disorders.

Mechanism of Action

Tizanidine acts as a selective **α2-adrenergic receptor agonist** in the central nervous system. By stimulating these receptors in the spinal cord, it inhibits the release of excitatory amino acids and suppresses polysynaptic reflex activity, leading to reduced spasticity and muscle tone without significant loss of muscle strength.

Pharmacodynamics

- Reduces spasticity by increasing presynaptic inhibition of motor neurons.
- Produces muscle relaxation and mild sedative effects.
- Has less impact on cardiovascular function compared to clonidine but may still lower blood pressure.

Pharmacokinetics

- **Absorption:** Rapidly absorbed orally, but bioavailability ~40% due to first-pass metabolism.
- **Distribution:** Widely distributed; ~30% protein binding.
- **Metabolism:** Extensively metabolized in the liver via CYP1A2.
- **Elimination half-life:** ~2.5 hours.
- **Excretion:** Metabolites primarily excreted in urine (~60%).

Uses

- Management of muscle spasticity due to multiple sclerosis, spinal cord injury, or stroke.
- Sometimes used off-label for chronic pain syndromes and fibromyalgia.

Dosage

- **Initial dose:** 2 mg orally, up to 3 times daily.
- **Titration:** May increase by 2–4 mg per dose at weekly intervals.
- **Maximum dose:** 36 mg per day, divided in multiple doses.

Side Effects

- Common: Drowsiness, dizziness, dry mouth, weakness, fatigue, hypotension.
- Less common: Hallucinations, hepatotoxicity, bradycardia.
- Rare but serious: Severe hypotension, liver failure.

Drug Interactions

- **Contraindicated with strong CYP1A2 inhibitors** (e.g., fluvoxamine, ciprofloxacin) – can cause dangerous increases in plasma concentration.
- May interact with antihypertensives, increasing risk of hypotension.
- Alcohol and CNS depressants enhance sedative effects.

Storage

- Store at **20–25 °C (68–77 °F)**.
- Keep in a dry place, away from moisture and light.
- Keep out of reach of children.

2. Materials and Methods

Table.1: List of Materials Used

Name of the Material	Source
Tizanidine	Shandong Xinhua Pharmaceutical Co., Ltd, China
Avicel PH 101	Colorcon
Avicel PH 102	Colorcon
Aerosil	Aqualon
Crospovidone	Colorcon
Sodium starch glycolate	Colorcon
Lactose	DMV- Fonterra excipients
Dicalcium Phosphate	Merck laboratories
AcDiSol	Merck laboratories
Polyethyleneglycol	Synero
Propyleneglycol	Colorcon

Table.2: List of Equipment's used

Name of the Equipment	Manufacturer
Electronic weighing balance	Wensar
Friabilator	Franz
Compression machine	Labindia, Mumbai, India
Tablet hardness tester	Labindia, Mumbai, India
UV	Per kin Elmer, United States of America.
Dissolution apparatus	Labman scientific instruments

Preformulation studies:

Pre formulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system.

Drug-Excipients compatibility studies: Drug Excipients compatibility studies were carried out by mixing the drug with various excipients in different proportions (in 1:1 ratio were prepared to have maximum likelihood interaction between them) was placed in a vial, and closed with rubber stopper and sealed properly. Studies were carried out in glass vials at Accelerated conditions, 40º C ± 2° C / 75% RH ± 5 % RH and A storage period of 12 weeks. After storage, the sample was compared with control at 2-8°C and

observed physically for liquefaction, caking, and, discoloration. To investigate the possible physical and chemical interactions between the drug and excipient Differential scanning calorimetry studies were performed.2-3 mg of pure Tizanidine, Avicel PH 200, Aerosil PH 200 and liquisolid system physical mixture were weighed and were sealed in a 40-µl aluminum pans. The scanning rate of sample was 5^0 C/ min under nitrogen atmosphere at a heating range from 5^0 C to 150^0 C.

Analytical method development for Tizanidine:

a) Determination of absorption maxima

A spectrum of the working standards was obtained by scanning from 200-400nm against the reagent blank to fix absorption maxima. The Tmax was found to be 284nm. Hence all further investigations were carried out at the same wavelength.

b)Preparation of standard graph in 0.1 N HCl

100 mg of Tizanidine was dissolved in methanol 5 ml, volumetric flask make upto 100 ml of 0.1 N hydrochloric acid, from this primary stock 10 ml was transferred to another volumetric flask made up to 100ml with 0.1 N HCl, from this secondary stock was taken separately and made up to 10 ml with 0.1 N hydrochloric acid, to produce 10, 20, 30, 40, 50, 60, 70, 80 µg/ml respectively. The absorbance was measured at 284 nm by using a UV spectophotometer.

Preformulation studies:

Solubility studies

For the selection of best nonvolatile solvents solubility studies are used, in this procedure, pure drug was dissolved in five different nonvolatile solvents. Excess amount of pure drug was adding to the nonvolatile solvents. From this obtained saturation solution were shaking on the rotary shaker for 48 hours at 25 ^{0}C under constant vibration. After 48 hours period the saturated solution were filtered through a filter paper, and analyzed by UV spectrophotometer. The liquisolid tablets contain a solution of the drug in suitable solvent, the drug surface available for dissolution is tremendously increased.

Calculation of loading factor (L_f)

Loading factors were calculated for different carriers, using various solvents. By using L_f = W/Q formula (W: Amount of liquid medication and Q: Amount of carrier material), the drug loading factors were obtained and used for calculating the amount of carrier and coating materials in each formulation. The results showed that if the viscosity of the solvent is higher, lower amounts of carrier and coating materials are needed to produce flowable powder.

Formulation Development:

Preparation of liquisolid tablets

Preparation of drug solution:

For the preparation of liquisolid compacts of Tizanidine, a non-volatile solvent is chosen for dissolving the drug. From the results of solubility studies and evaluation of flow properties, liquisolid powders containing PEG 400 as the liquid medicament, Avicel ^{PH} 101 as carrier and Aerosil PH 200 as the coating material are selected for the preparation of liquisolid compacts. Various ratios of carrier to coating materials are selected. According to solubility of Tizanidine, desired quantities of drug and PEG 400 were accurately weighed in a beaker and then stirred with constantly, until a homogenous drug solution was obtained. Selected amounts (W) of the resultant liquid medication were incorporated into calculated quantities of carrier contained in a mortar.

Mixing:

The mixing procedure was conducted in three stages. During the first stage, the system was blended at an approximate mixing rate of one rotation/sec for approximately one minute in order to evenly distribute the liquid medication into the powder. In the second mixing stage, calculated quantities of coating material was added to the system and blended for 2 min. the liquid/powder admixture was evenly spread as a uniform layer on the surfaces of the mortar and left standing for approximately 5min to allow the drug solution to be absorbed in interior of the powder particles.

In the third stage, the powder was scraped off the mortar surfaces by means of aluminium spatula and then blended with a calculated quantity of disintegrant (5%) for another 30sec, in a manner similar to the one used in the first stage, producing the final liquisolid formulation to be compressed. The tablets were prepared by compressing the thoroughly mixed materials using 6.4 mm round, flat and plain punches on a single station tablet machine (Cadmach India). The thickness of the tablet was 3.6mm.

Strategy 1: Using 10%, 20%, 30%, 40% concentration of drug in PEG400, Aviel PH 200, Avicel PH 101 as carrier material and with different carrier and coating material ratios batches were developed and evaluated.

Table 3: Composition of liquisolid tablets

Formulation	Tizanidine conc.in PEG 400	R	L_f	Avicel PH 200 (mg)	Avicel ®PH 101(mg)	Aerosil PH 200(mg)	Total tablet weight(mg)
F1	10%	5	0.312	400	-	80.0	635.0
F2		10	0.312	400	-	40.0	592.5
F3		15	0.312	400	-	26.5	579.0
F4		20	0.312	400	-	20.0	572.5
F5	20%	5	0.312	200	-	40.0	317.5
F6		10	0.312	200	-	20.0	295.5
F7		15	0.312	200	-	13.2	288.2
F8		20	0.312	200	-	10.0	285.0
F9	30%	5	0.208	200	-	40.0	294.1
F10		10	0.208	200	-	20.0	274.1
F11		15	0.208	200	-	13.2	267.3

F12		20	0.208	200	-	10.0	264.1
F13	10%	5	0.312	-	400	80.0	635.0
F14		10	0.312	-	400	40.0	592.5
F15		15	0.312	-	400	26.5	579.0
F16		20	0.312	-	400	20.0	572.5
F17	20%	5	0.312	-	200	40.0	295.5
F18		10	0.312	-	200	20.0	288.2
F19		15	0.312	-	200	13.2	300.2
F20		20	0.312	-	200	10.0	285.0
F21	30%	5	0.208	-	200	40.0	294.1
F22		10	0.208	-	200	20.0	274.1
F23		15	0.208	-	200	13.2	267.3
F24		20	0.208	-	200	10.0	264.1

L_f = Load factor; R= carrier and coating material ratio; PEG 400 =Poly ethylene glycol 400.

Table 4: Composition of liquisolid tablets

Formulation	Tizanidine Conc.in PEG200	R	Lf	Lactose (mg)	DCP (mg)	Avicel PH101 (mg)	Avicel PH200(mg)	Aerosil (mg)	Total Tablet Wt(mg)
F27	20%	5	0.312	200	-	-	-	40	317.5
F28	20%	5	0.312	-	200	-	-	40	317.5
F29	20%	5	0.312	-	-	200	-	40	317.5
F30	20%	5	0.312	-	-	-	200	40	317.5

L_f = Load factor; R= carrier and coating material ratio; PEG 200 =Poly ethylene glycol 200:

Table 5: Composition of liquisolid tablet

Formulation	Carvedilol conc.In PG	R	Lf	Lactose (mg)	DCP	Avicel PH 101(mg)	Avicel PH200(mg)	Aerosil PH 200(mg)	Total Tablet Weight(mg)
F31	20%	5	0.312	200	-	-	-	40	317.5
F32	20%	5	0.312	-	200	-	-	40	317.5
F33	20%	5	0.312	-	-	200	-	40	317.5
F34	20%	5	0.312	-	-	-	200	40	317.5

L_f = Load factor; R= carrier and coating material ratio; PG= Propylene Glycol.

Table 6: Composition of liquisolid tablets

Formulation	Tizanidine Conc.in Glycerine	R	Lf	Lactose (mg)	DCP (mg)	Avicel PH 101(mg)	Avicel PH 200(mg)	Aerosil PH200 (mg)	Total tablet weight(mg)
F35	20%	5	0.312	200	-	-	-	40	317.5
F36	20%	5	0.312	-	200	-	-	40	317.5
F37	20%	5	0.312	-	-	200	-	40	317.5
F38	20%	5	0.312	-	-	-	200	40	317.5

Lf = Load factor; R= carrier and coating material ratio**.**

Table 7: Composition of liquisolid tablets

Formulation	Tizanidine Conc.inPEG400	R	Lf	Avicel PH200(mg)	Aerosil (mg)	SSG (mg)	AciDi sol (mg)	Total Tablet Weight(mg)
F39	20%	5	0.312	200	40	5%	-	317.5
F40	20%	5	0.312	200	40	-	5%	317.5

L_f = Load factor; R= carrier and coating material ratio; PEG 400 =Poly ethylene glycol.

Table 8: Flow Properties and Corresponding Angle of Repose

Flow Property	Angle of Repose (^{0})
Excellent	25-30
Good	31-35
Fair- aid not needed	36-40
Passable-may hang up	41-45
Poor-must agitate, Vibrate	46-55
Very Poor	56-65
Very, very Poor	>66

Table 9: Scale of Flow ability

Compressibility Index (%)	Flow Character	Hausner Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

3. Results and Discussion

Construction of Standard calibration curve of Tizanidine in 6.8 phosphate buffer: Solution's absorbance had been evaluated at 263nm employing UV spectrophotometer, having 6.8 phosphate buffer as reference. Corresponding values has been listed in Table 20. Plotting of absorbance against concentration occurred, showing that measurements obeyed Beer's law within concentration ranging 2-10µg/mL.

Table 10: Standard Calibration graph values of Tizanidine in 6.8 phosphate buffer

S.No.	Conc. (µg/ml)	Absorbance
i	0	0
ii	2	0.128
iii	4	0.253
iv	6	0.387
v	8	0.509
vi	10	0.645

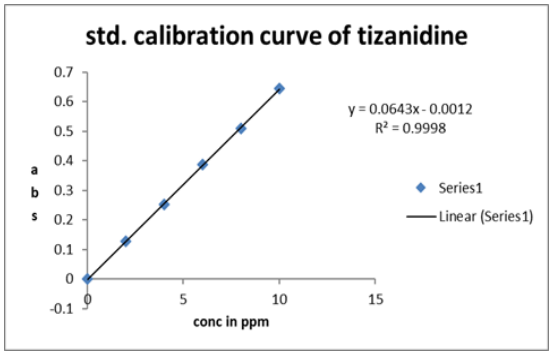

Fig.2: Standard calibration curve of Tizanidine in 6.8 phosphate buffer

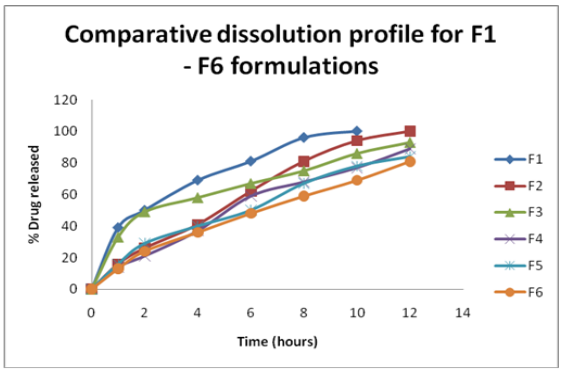

Fig.3: Comparative dissolution profile for F1-F6 formulations

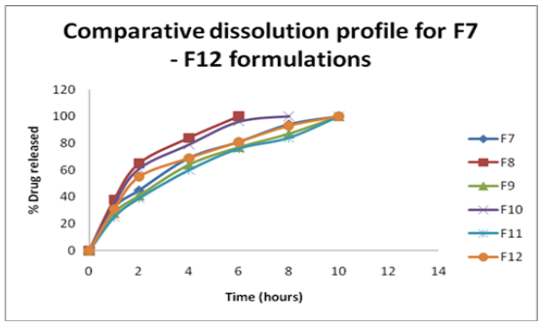

Fig.4: Comparative dissolution profile for F7-F8 formulations

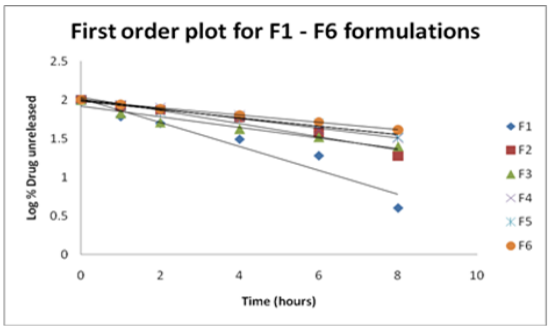

Fig.5: First order plot for F1 - F6 formulations

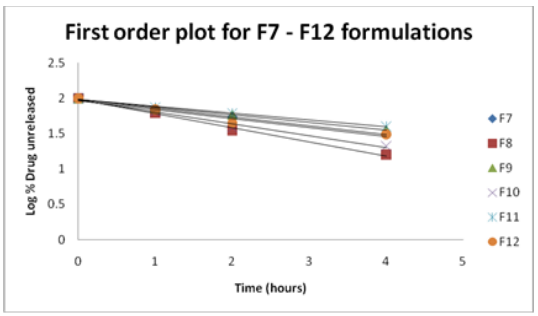

Fig.6: Higuchi plot for F7–F12 formulations

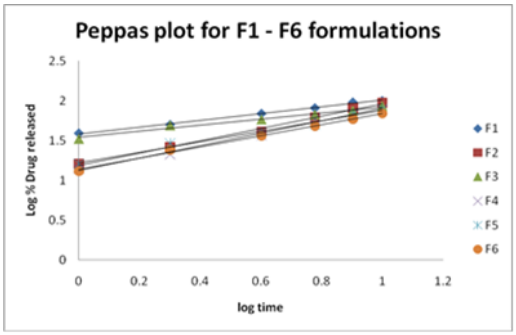

Fig.7: Korsmayerspepas plot for F1-F6 formulations

Table.11: Pre formulation studies of Tizanidine SR Tablets

S.NO	"Formulation Code	Bulk density (Kg/cm^3)	Tapped density (Kg/cm^3)	Cars index	Hausners ratio	Angle of repose
I	**F1**	0.43	0.52	17.3	1.41	12.62
II	**F2**	0.40	0.46	13.0	1.5	12.29
III	**F3**	0.50	0.58	13	1.16	11.58
IV	**F4**	0.44	0.51	13.7	1.25	9.29
V	**F5**	0.39	0.47	17.0	1.56	18.23
VI	**F6**	0.42	0.52	19.2	1.45	13.24
VII	**F7**	0.36	0.39	7.6	1.0	11.03
VIII	**F8**	0.41	0.50	18	1.5	17.4
IX	**F9**	0.39	0.48	18	1.23	11.96
X	**F10**	0.41	0.51	19.6	1.53	12.26
XI	**F11**	0.44	0.52	15.3	1.40	13.62
XII	**F12**	0.41	0.45	8.8	1.0	11.85"

Table.12: Post formulation studies of Tizanidine SR Tablets

S.No	Formulation Code	% weight variation	Thickness (mm)	% friability	% Drug Content	Hardness (Kg/cm^2)
1	F1	pass	3.66±0.11	0.22	102.0 ±1.1	6.68 ±0.17
2	F2	pass	3.93±0.15	0.15	101.3 ±1.5	6.13 ±0.15
3	F3	pass	4.06±0.057	0.12	99.8±1.3	6.58 ±0.13
4	F4	pass	4.81±0.1	0.43	101.7 ±0.8	6.98 ±0.04
5	F5	pass	4.03±0.05	0.32	100.6±1.2	6.63 ±0.05
6	F6	pass	3.83±0.15	0.14	98.9 ±2.1	6.2 ±0.02
7	F7	pass	4.93±0.05	0.20	99.2± 1.7	6.7 ±0.10
8	F8	pass	5.26±0.1	0.33	99.5± 1.4	6.93 ±0.05
9	F9	pass	4.02±0.2	0.18	99.2±1.3	6.39 ±0.02
10	F10	pass	4.48±0.14	0.21	100.3 ±1.4	6.86 ±0.03
11	F11	pass	4.91±0.18	0.32	101.2± 1.6	6.72 ±0.12
12	F12	pass	5.14±0.12	0.16	100.3 ±1.8	5.89 ±0.13"

Table.13: Dissolution profile

S.NO.	"Parameter	Details
I	Medium	6.8phosphate buffer
II	Dissolution apparatus	USP -Type II (paddle)
III	Temperature	37±0.5ºC
IV	Analytical method	Ultraviolet Visible Spectroscopy
V	Speed	50rpm
VI	Time points	1,2,4,6,8,10 &12hr"
VII	Sample volume withdrawn	5ml
VIII	Volume	900ml
IX	λ_{max}	263nm

Table.14: In-vitro Dissolution results of Formulation trails

TIME (hrs)	% Drug Released											
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
0	0	**0**	0	0	0	0	0	0	0	0	0	0
1	39	**16**	33	14	16	13	32	38	28	35	25	31
2	50	**26**	49	21	29	24	45	65	41	61	39	55
4	69	**41**	58	37	40	36	69	84	64	79	60	69
6	81	**62**	67	59	50	48	81	100	77	96	76	81
8	96	**81**	75	68	67	59	94		87	100	84	93
10	100	**94**	86	77	78	69	100		100		100	100
12		**100**	93	89	84	81						

Table.15: R^2 value and n result table

Formulation Code	R^2 value				n value
	Zero order	First order	Higuchi plot	Peppas plot	
F1	0.875	0.932	0.992	0.995	0.424
F2	0.980	0.879	0.962	0.994	0.767
F3	0.863	0.94	0.984	0.98	0.385
F4	0.977	0.986	0.965	0.99	0.778
F5	0.969	0.975	0.979	0.988	0.657
F6	0.982	0.996	0.975	0.995	0.707
F7	0.907	0.992	0.996	0.995	0.532
F8	0.882	0.993	0.991	0.967	0.526
F9	0.928	0.994	0.997	0.997	0.575
F10	0.854	0.987	0.982	0.968	0.546
F11	0.943	0.994	0.993	0.999	0.621
F12	0.869	0.961	0.988	0.949	0.519

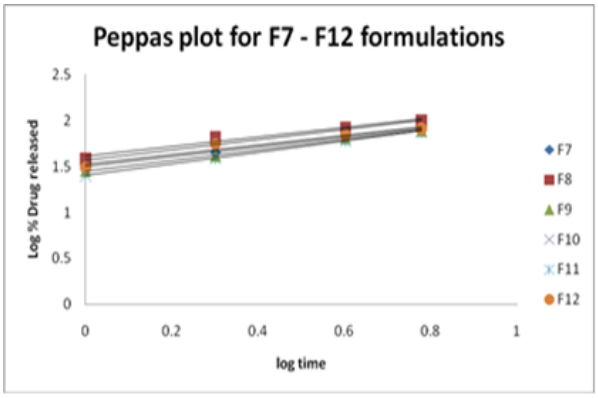

Fig.8: Korsmayers pepas plot for F7-F12 formulations

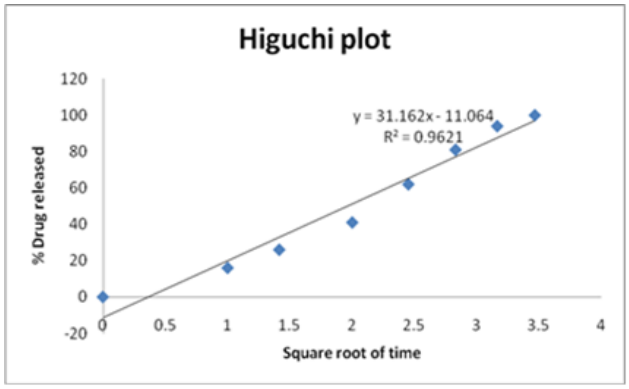

Fig.11: Higuchi plot for F2 formulation

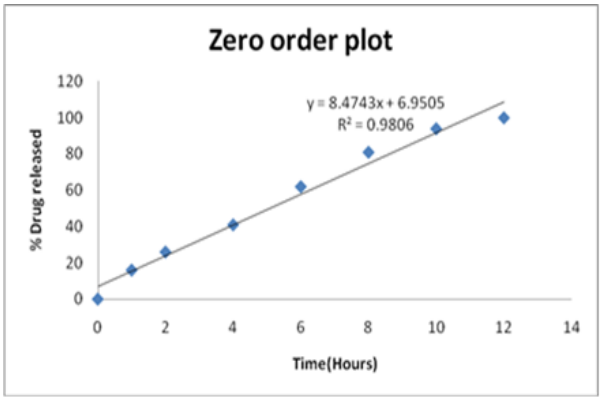

Fig.9: Zero order plot for F2 formulation

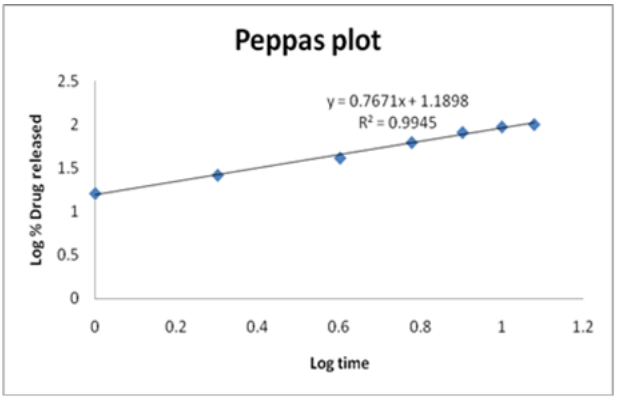

Fig.12: Peppas plot for F2 formulation

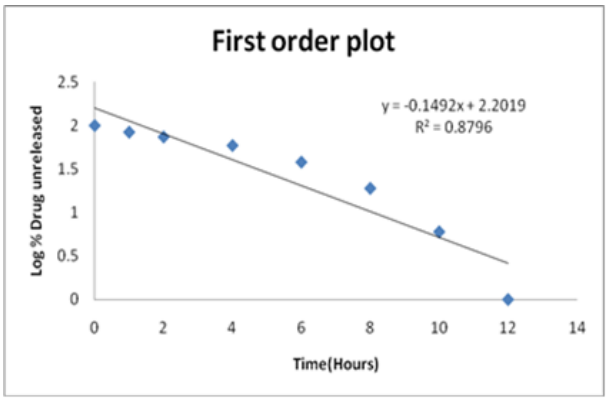

Fig.10: First order plot for F2 formulation

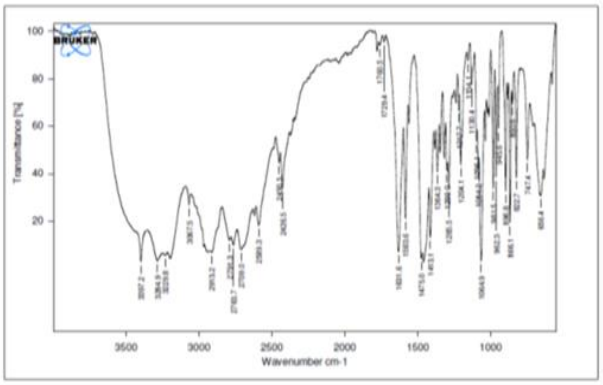

Fig.13: FTIR graph for Tizanidine pure drug

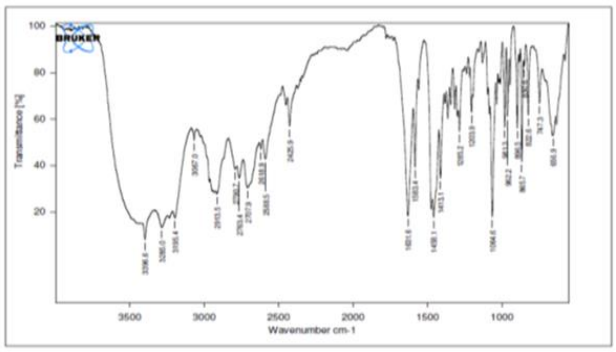

Fig.14: FTIR graph for formulation F2

4. Conclusion

The approach of the present study was to make a comparative evaluation among these polymers (Xanthum gum and Tragacanth) and to assess the effect of physico-chemical nature of the active ingredients on the drug release profile by liquid solid compact method using PEG400 and Tween 80. The angle of repose, compressibility index and sieve analysis results shown that the formulation is suitable for liquid solid compaction method. This study have been showed that Tizanidine could be used in sustained release drug delivery system by formulating it has sustained drug delivery system, provides extend duration of action in therapeutic range without reaching toxic levels as in the case of conventional dosage forms. These dosage forms have the ability to reduce the dosing frequency and increasing. By the results we can confirm that order of drug release first order and the mechanism of drug release from sustained release Tablets is Higuchi model. Success of the In vitro drug release studies recommends the product for further In vivo studies, it may improve patient compliance.

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