



Development and Optimization of Orally Dissolving Film of Zolpidem Tartarate

Vinay Umesh Rao*, P.Sai Sruthi, M. Sudhakar, K.Kishore Kumar

Malla Reddy College of Pharmacy, Maisammaguda, Post Dhulapally, Secunderabad 500014, India.

Date of Receipt- 18/07/2013
Date of Revision- 22/07/2013
Date of Acceptance- 01/08/2013

Address for Correspondence

Malla Reddy College of Pharmacy,
Maisammaguda, Post
Dhulapally,
Secunderabad
500014, India.

E-mail: vinayrao68@gmail.com

ABSTRACT

Zolpidem tartarate (ZT) is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. The objective of this research was to prepare oral dissolving films (ODF) containing ZT. Different combinations of polymers and plasticizers were evaluated for optimizing the physical properties and the in vitro drug release. Films were prepared and subjected to various physicochemical evaluations and in vitro dissolution studies. The film prepared using HPMC E15 (F4) with 1:1 ratio of drug and polymer with glycerol as plasticizer were considered to have acceptable physical properties, disintegration time of below 60 seconds and > 85% of drug release within 5 minutes and hence were considered as optimum.

Keywords: Zolpidem Tartarate (ZT), oral dissolving film (ODF), HPMC E15, in vitro drug release.

INTRODUCTION

Insomnia, or sleeplessness, is a sleep disorder in which there is an inability to fall asleep or to stay a sleep as long as desired. Insomnia is most often thought of as both a sign and a symptom that can accompany several sleeps, medical, and psychiatric disorders characterized by a persistent difficulty falling asleep and/or staying asleep or sleep of poor quality^{1,2}.

ZT is a prescription medication used for the treatment of insomnia and some brain disorders. It is a short-acting non benzodiazepine hypnotic of the imidazopyridine class that potentiates GABA, an inhibitory neurotransmitter, by binding

to GABA_A receptors at the same location as benzodiazepines. It works quickly, usually within 15 minutes, and has a short half-life of two to three hours. ZT is used for short-term (usually about two to six weeks) treatment of insomnia. It has not proven effective in maintaining sleep and is more used for sleep initiation problems^{3,4}.

Rapidly disintegrating or quick disintegrating dosage forms have acquired great importance in the pharmaceutical industry⁵⁻⁷ due to their unique properties and advantages. They undergo disintegration in the salivary fluids of the oral cavity within a minute, where they release the active

pharmaceutical ingredient. The major amount of the active pharmaceutical ingredient is swallowed orally with the saliva where subsequent absorption takes place in the gastro-intestinal tract^{8,9}. The problem of swallowing tablets is more evident in geriatric and paediatric patients, as well as travelling patients who may not have ready access to water¹⁰⁻¹³. So, fast-dissolving drug-delivery systems came into existence in the late 1970's as an alternative to tablets, capsules and syrups for paediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms^{14,15}.

Apart from being available as a conventional immediate release tablet, to be taken before going to bed for sleep initiation, ZT is also available as a sublingual tablet to be taken in between the sleep cycle in order to maintain the duration of sleep. This product is available as a 3.5 mg sublingual tablet (Intermezzo)¹⁶⁻¹⁸. The focus of the current work is to develop a fast disintegrating thin film dosage form as a better alternative to sublingual tablet. Anticipated patient convenience for thin film may be significantly better than for sublingual tablets^{19,20}. The type and concentration of polymer and the plasticizer were optimized with respect to physical properties of the films, disintegration time and in vitro dissolution studies. The target product profile is given in TABLE 1.

MATERIALS AND METHOD

Materials

Zolpidem tartarate (EMCO Industries, Hyderabad, India). HPMC E5 (Dow Chemicals, USA), HPMC E15, PVA (Dow Chemicals, USA), Glycerol AR grade (Merck, India), PEG 400 IP (Merck India). All other chemicals and reagents used were of AR grade from Merck India. Purified water USP (Millipore system) was used where indicated.

Methods

Preparation of placebo formulations

The placebo film formulations are given in TABLE 2 and the process is shown in FIGURE 1¹⁹.

Evaluation parameters of placebo formulations

The films were evaluated for drying time, average weight, thickness, tensile strength, folding endurance and disintegration time^{21,22}. The results of the evaluation were given in TABLE 3.

Preparation of drug loaded formulations

The composition for the drug loaded films is given in TABLE 4. The procedure followed was similar to the flow chart (FIGURE 1). The ZT was added to the polymer solution and sonicated for 15 minutes till the drug was completely dissolved. The drug loaded films were evaluated for average weight, thickness, tensile strength, folding endurance, disintegration time and in vitro dissolution studies. The data for physical parameters, assay and content uniformity is given in TABLE 5.

RESULTS AND DISCUSSION

Placebo Films

The drying time for PVA based films were unacceptably long (>24 hours). Also these films were much inferior to HPMC based films in terms of disintegration time and thickness values.

The HPMC E5 and E15 films showed acceptable values for the evaluated parameters and were selected for the drug loading studies. Among the films made of HPMC E5 5fl (1:1) formulation showed poor tensile strength. So, it was not selected for drug loading studies.

Drug Loaded Films

The tensile strength and disintegration time of all films was compared in FIGURE 2 and FIGURE 3. It was observed that both these parameters had a strong dependency on the drug to polymer ratio as well as on the viscosity of the polymer. The formulation using E15 at 1:1 ratio (F4) shows the most promising results.

In vitro release studies of various formulations were performed using pH 6.8 phosphate buffer²³ as dissolution medium and measuring drug concentration spectrophotometrically at 240 nm. The dissolution profile is shown in FIGURE 4 and FIGURE 5. All formulations achieve 80% (Q) release within 10 minutes. Dissolution at 2 minutes (D2) time point is compared in FIGURE 6. There is a marginal but not significant difference in dissolution between different compositions. The dissolution profile (% Drug release in 2mins) Vs disintegration time (seconds) is shown in FIGURE 7.

CONCLUSIONS

Quick disintegrating oral films of ZT were successfully formulated using HPMC E5 and E15 formulations. The final composition optimized was drug to HPMC E15 ratio of 1:1, glycerol concentration of 15% w/w of polymer. The film had acceptable physical properties, assay and content uniformity values. The average disintegration time for the optimized film was within 60 seconds and greater than 80% of the drug was released within 2 minutes. A prototype film is shown in FIGURE 8.

REFERENCES

- Golub, R. M, "Insomnia". *JAMA: the Journal of the American Medical Association*; 307 (24): 2653–2654.
- Roth, T, "Insomnia: Definition, prevalence, etiology, and consequences". *Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine*. **3** (5 Suppl): S7–10.
- Lemmer B, "The sleep-wake cycle and sleeping pills". *Physiol. Behav.* **90** (2–3): 285–93.
- Rosenberg, RP. "Sleep maintenance insomnia: strengths and weaknesses of current pharmacologic therapies." *Annals of Clinical Psychiatry*. **18** (1): 49–56.
- Renuka Mishra and Avani Amin, Formulation and Characterization of Rapidly Dissolving Films of Cetrizine hydrochloride using Pullulan as a Film Forming Agent, *Indian Journal of Pharmaceutical Education and Research: IJPER*, Jan-Mar, 2011/ Vol 45/ Issue 1.
- Liang AC, Chen LH. Fast Dissolving Intraoral Drug Delivery Systems. *Exp. Opin. Ther. Patents* 2001; 11(6):981–6.
- Borsadia S, O'Halloran D, Osborne JL. Quick Dissolving Films-A Novel Approach to Drug Delivery. *Drug Delivery Technology* 2003; 3(3):63-66.
- Klancke J. Dissolution Testing of Orally Disintegrating Tablets. *Dissolution Technologies* 2003; 10(2):6–8.
- Parakh SR, Gothoskar AV. Review of Mouth Dissolving Tablet Technologies. *Pharm Tech* 2003; 27(11):92–100.
- Habib W, Pritchard JF, Bozigian HP, Gooding AE, Griffin RH, Mitchell R, Bjurstrom T, Panella TL, Huang AT, Hansen LA, Fast-dissolve drug delivery system. *Crit. Rev. Ther. Drug Carrier Syst.* **17**: 2000: 61–72.
- Liang C A, Chen HL, Fast dissolving intraoral drug delivery systems. *Expert Opin. Ther. Patents*. **11**: 2001: 981-986.
- Anderson O, Zweidorff OK, Hjelde T, Rodland EA, Problems when swallowing tablets. *Tidsskr NorLaegeforen*. **115**: 1995: 947-949.
- Joseph F Standing, Catherine Tuleu, Pediatric formulations-Getting to the heart of the problem. *International Journal of Pharmaceutics*. **300**: 2005: 56–66.
- Goel Honey, Rai Parshuram, Rana Vikas, Tiwary K Ashok , Orally Disintegration systems: Innovations in formulation and Technology. *Recent Patents on Drug Delivery & Formulation*. **2**: 2008: 258-274.

15. Bhowmik Debjit, Chiranjib B, Krishnakanth, Pankaj, Margret R Chandira, Fast Dissolving Tablet: An Overview. *Journal of Chemical and Pharmaceutical Research*. 1(1): 2009: 163-177.
16. Jeffrey, Susan. "FDA Approves Intermezzo, First Drug for Early Awakening". Retrieved 26 November 2011.
17. Roth T, Hull SG, Lankford DA, Rosenberg R, Scharf MB; Intermezzo Study Group Low-dose sublingual zolpidem tartrate is associated with dose-related improvement in sleep onset and duration in insomnia characterized by middle-of-the-night (MOTN) awakenings. *Sleep* 2008 Sep; 31(9):1277-84.
18. www.intermezzorx.com/hcp/
19. Bhupinder Bhyan, Saritha Jangra, Mandeep Kaur, Harmanpreet Singh; Orally fast dissolving films: innovations in formulation and technology. *ISSN 0976 – 044X*, Volume 9, Issue 2, July – August 2011; Article-009.
20. Zhang H, Zhang J and Streisand JB: Oral mucosal drug delivery: clinical pharmacokinetics and therapeutic applications. *Clinical Pharmacokinetics* 2002; 41: 661-680.
21. American standard of testing and materials. ASTM D-1004-08. Standard test method for tear resistance (Graves Tear) of plastic film and sheeting.
22. Dinge A and Nagarsenker M. Formulation and evaluation of fast dissolving films of delivery of Triclosan to the oral cavity. *AAPS Pharm Tech*. 2008, 9(2), 349-56.
23. B.pamula, Reddy, Varma, M.Mohan, Raju, D.Basava, Venugopal Rao.G. Formulation And characterization of Zolpidem tartarate oral fast dissolving films. *Advanced science, engineering and medicine*.2013; 5(8):771-77.

Table 1. Target Product Profile

S. No.	Parameters	Specifications
1	Tensile strength of film	Not less than 1 N/cm ²
2	% elongation	35mm to 55 mm%
3	Thickness	0.1 ±0.03 mm
4	Folding endurance	>100 folds
5	Unit surface area (for 3.5 mg drug load)	2 ±0.02 cm ²
6	Average weight of 1 unit film	18 ± 2 mg
7	Drug Content (mg/2cm ²)	3.5 mg (3.325-3.605)
7	Content uniformity by assay method (for 10 units)	85 to 115% of average
8	Disintegration time (in 5 ml water at room temperature)	NMT 180 seconds
9	In vitro drug release	Not less than 80% (Q) in 15 minutes in 500 ml of ph 6.8 buffer.

Table 2. Placebo Film Formulations

INGREDIENTS	5f1	5f2	5f3	5f4	15f1	15f2	15f3	15f4	Pf1	Pf2	Pf3
HPMC E5(mg)	62.5	125	187.5	250	-	-	-	-	-	-	-
HPMC E15(mg)	-	-	-	-	62.5	125	187.5	250	-	-	-
PVA(mg)	-	-	-	-	-	-	-	-	125	187.5	250
GLYCEROL (mg)	9.38	18	28.1	37.5	9.38	18.7	28.1	37.5	18.7	28.1	37.5
MANNITOL (mg)	100	100	100	100	100	100	100	100	100	100	100
DISTILLED WATER (ml)	10	10	10	10	10	10	10	10	10	10	10

Table 3. Evaluation Parameters of HPMC E5, HPMC E15, PVA

Evaluation Parameters	HPMC E 5				HPMC E 15				PVA		
	5f1	5f2	5f3	5f4	15f1	15f2	15f3	15f4	Pf1	Pf2	Pf3
Drying time(hrs)	16-24	16-24	16-24	16-24	16-24	16-24	16-24	16-24	>24	>24	>24
Disintegration time (seconds)	22±5	52±2	59±3	63±2	47±3	58±1	66±2	77±2	130±2	152±1	179±3
Folding endurance (No. of Folds)	28±4	119±1	129±2	134±1	110±3	122±3	133±1	140±1	162±4	184±2	191±5
Average weight(mg)	4±3	10±4	14±3	18±2	8.5±3	14±3	17±2	20±1	48±4	61±3	70±2
Thickness (mm)	0.009±0.02	0.07±0.03	0.1±0.01	0.121±0.02	0.06±0.01	0.105±0.01	0.128±0.02	0.141±0.01	0.182±0.02	0.206±0.01	0.311±0.02
Tensile strength (N/cm ²)	0.02±0.04	0.99±0.05	1.65±0.04	1.99±0.02	1.74±0.03	1.99±0.06	2.28±0.02	2.78±0.02	3.78±0.01	4.03±0.03	4.97±0.02

Table 4. Drug Loaded Zt Films

Ingredients	HPMC E5			HPMC E 15			
	F1	F2	F3	F4	F5	F6	F7
Drug(mg)	62.5	62.5	62.5	62.5	62.5	62.5	62.5
Polymer (mg)	125	187.5	250	62.5	125	187.5	250
Glycerol (mg)	18.7	28.1	37.5	9.38	18.7	28.1	37.5
Mannitol(mg)	100	100	100	100	100	100	100
Flavour	5%	5%	5%	5%	5%	5%	5%
Dist. Water(ml)	10	10	10	10	10	10	10

Table 5. Evaluation Parameters of Drug Loaded Formulations

Formulation Code	Average Weight (mg)	Thickness (mm)	Folding Endurance	Disintegrate-on Time (seconds)	Tensile Strength (N/cm ²)	% Elongation	Drug Content (mg)	Content Uniformity (%)
F1	16.5±0.3	0.082±0.01	119±1	52±1	1.03±0.05	25.44±0.68	3.52	103-105
F2	18±0.4	0.109±0.02	130.3±9	60±2	1.87±0.01	49.5±0.62	3.48	89-101
F3	19.9±0.8	0.126±0.01	136.3±3	65±2	2.23±0.04	65.5±0.50	3.39	83-91
F4	14.7±0.7	0.081±0.02	112±3	49±2	1.88±0.02	25.62±0.82	3.57	100-104
F5	19±2.6	0.113±0.01	122±2	58±1	2.03±0.07	38.94±0.83	3.60	85-93
F6	21.4±0.4	0.134±0.05	135.3±2	69±2	2.43±0.02	69.2±0.36	3.46	85-87
F7	22±2	0.157±0.02	140.6±1	78±1	3.02±0.01	71.6±0.23	3.35	90-98

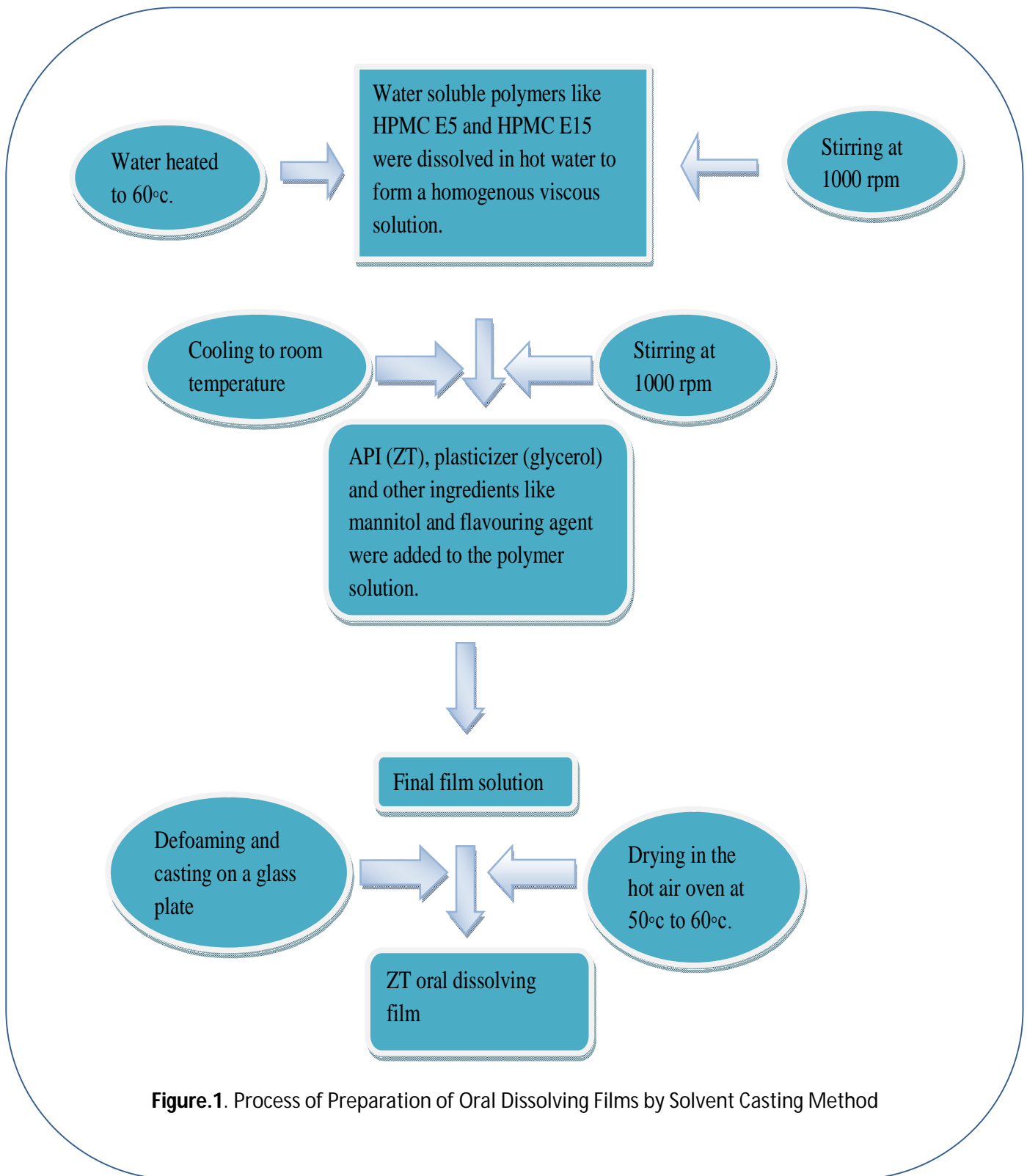


Figure.1. Process of Preparation of Oral Dissolving Films by Solvent Casting Method

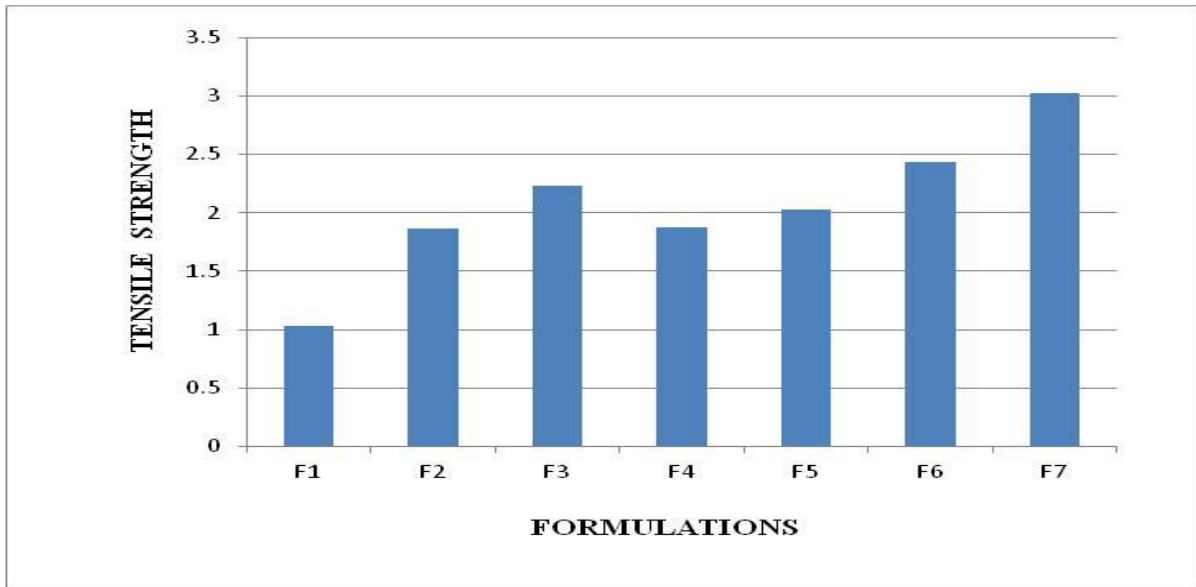


Figure.2. Tensile Strength in N/cm²

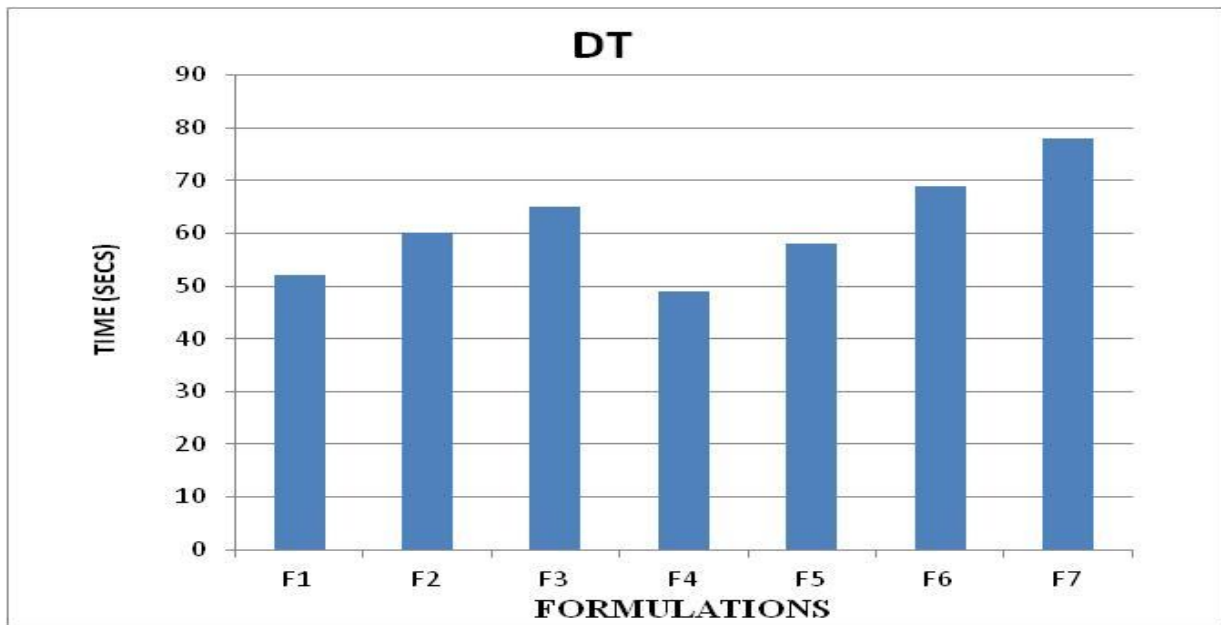


Figure.3. Disintegration Time (DT)

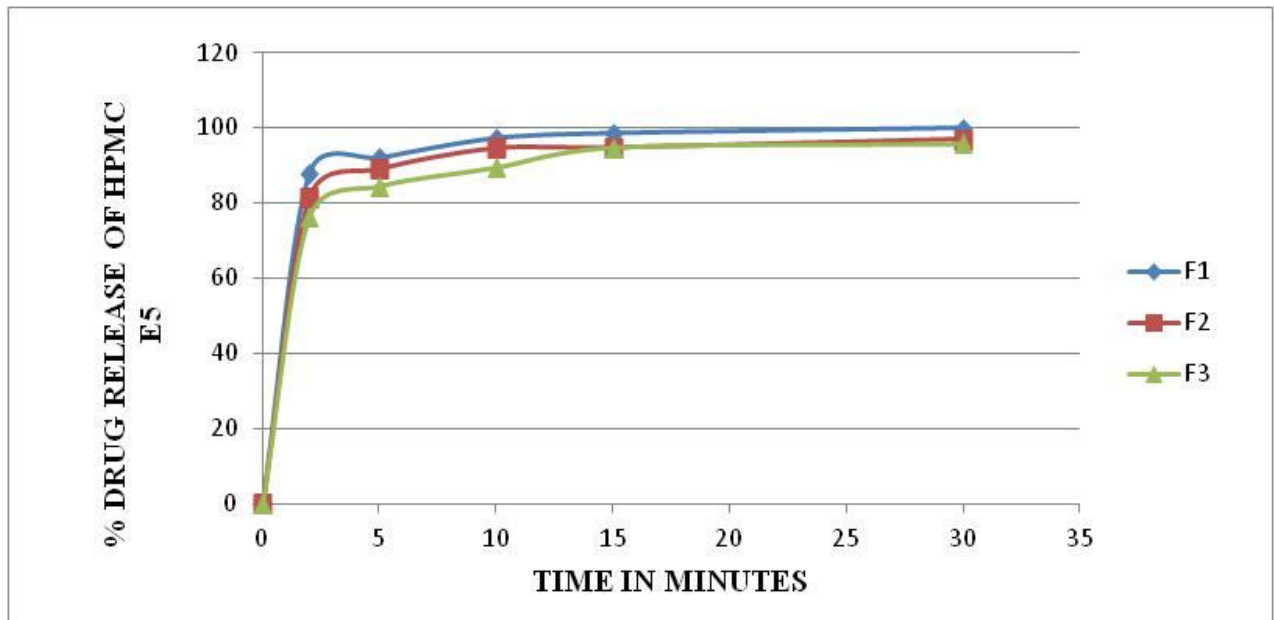


Figure.4. *In vitro* Dissolution Studies of HPMC E 5

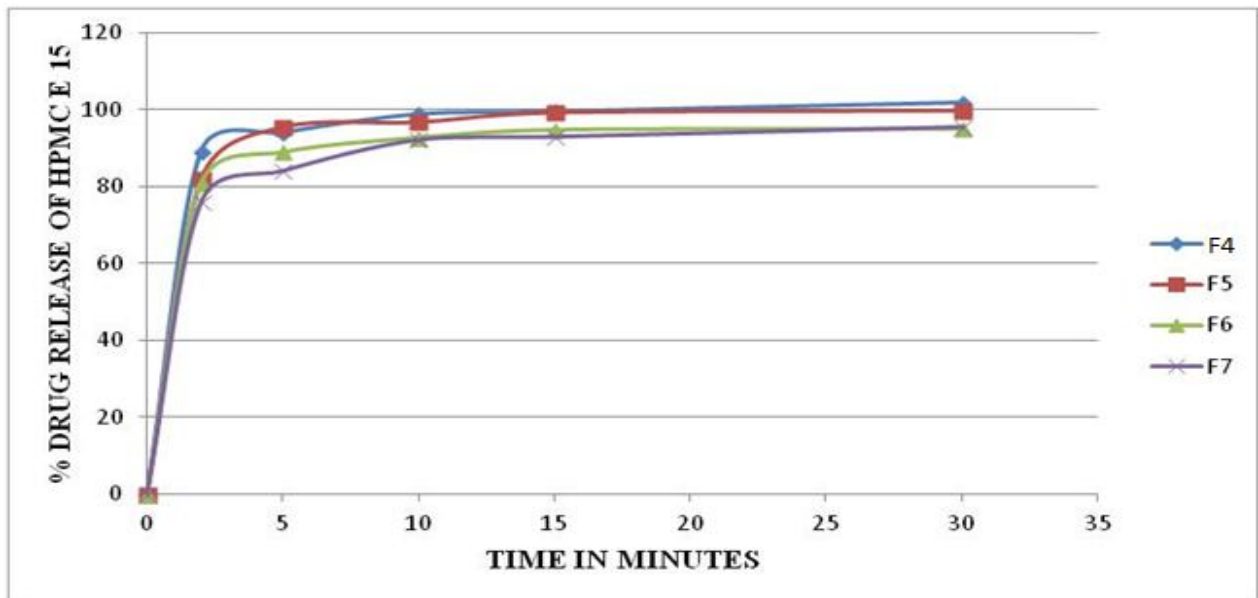


Figure.5. *In vitro* Dissolution Studies of HPMC E15

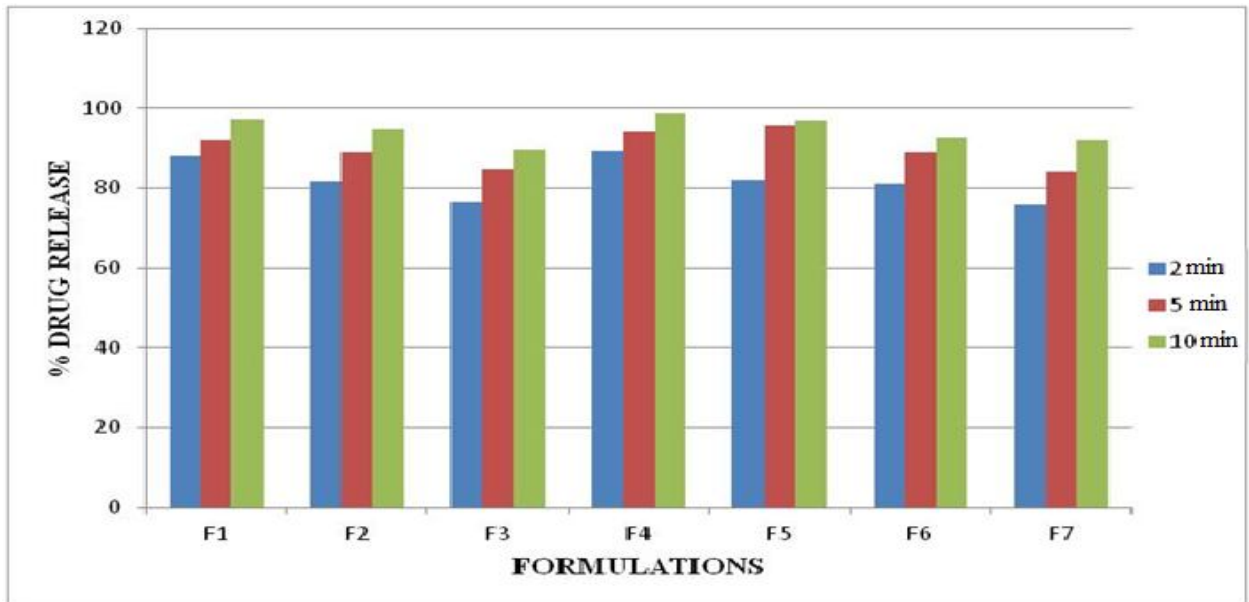


Figure.6. Comparative Dissolution Studies of HPMC E 5 and HPMC E15 at 2, 5 and 10 Minutes

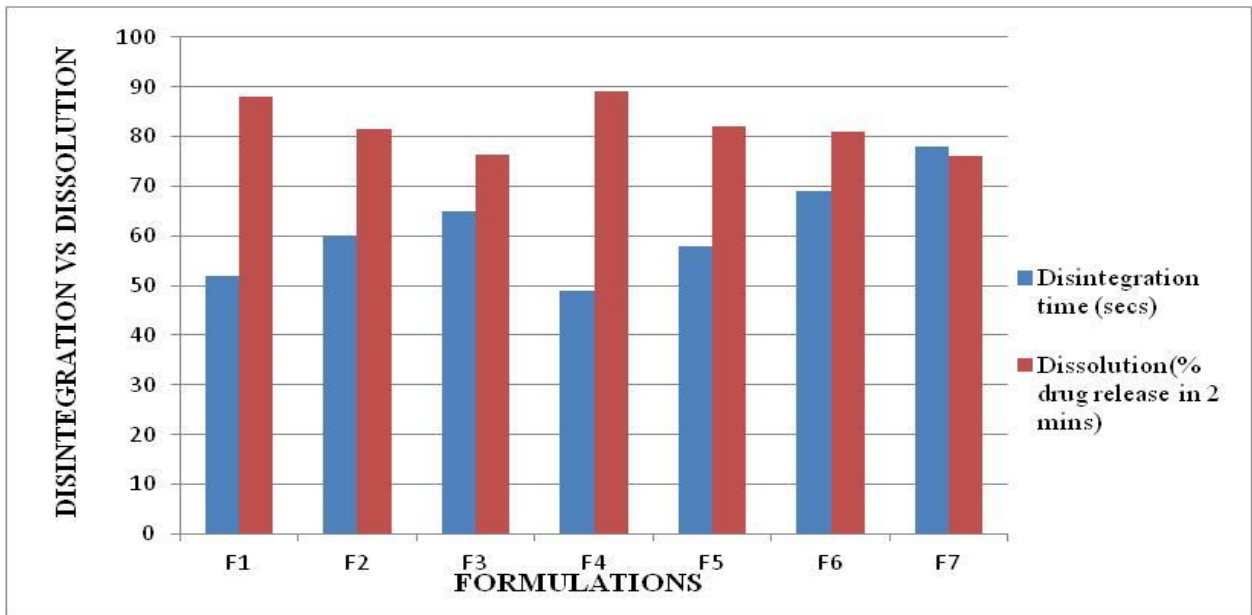


Figure.7. Disintegration Time (seconds) Vs Dissolution Profile (% Drug Release in 2 mins)



Figure.8. Quick Dissolving Oral Film (F4)