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Formulation Development and Evaluation of Immediate Release Tablet of Topiramateanti Epileptic Drug

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ABSTRACT:

The core tablet of topiramate was prepared using wet granulation containing CCS Na,MCC,DPA,Povidone k30. Opadry White was used for coating the core tablets. Total 16 batches were formulated.In that last 6 batches were optimized by process parameters like kneading time, lubrication time and by sizing.These formulations were evaluated for physical parameters of tablet, drug-excipient compatibility study, and in- vitro drug release study.The optimize formulation F8 release profile was match with marketed formulation and release rate was maximum than other batches.Stability study of the optimized formulation indicates no significant differences in release profile and drug content after a period of one to three month.Immediate release dosage form of API was formulated using Croscarmellose Sodium as superdisintegrant. Among all the formulations, F8 formulation was finally optimized. It is fulfilling all the parameters satisfactorily. It has shown excellent thickness, hardness, in vitro disintegration and *in vitro* dissolution.

Keywords: Topiramateanti, Croscarmellosesodium, Immediate release, Opadry white.

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INTRODUCTION:

Immediate Release Tablet [1,2,3]

Pharmaceutical products designed for oral delivery and currently available on the prescription and over-the-counter markets are mostly the immediate release type, which are designed for immediate release of drug for rapid absorption.

Disintegrating agents are substances routinely included in tablet formulations and in some hard shell capsule formulations to promote moisture penetration and dispersion of the matrix of the dosage form in dissolution fluids. Superdisintegrants improve disintegrant efficiency resulting in decreased use levels when compared to traditional disintegrants.

Traditionally, starch has been the disintegrant of choice in tablet formulation, and it is still widely used. For instance, starch generally has to be present at levels greater than 5% to adversely affect compatibility, especially in direct compression. Drug release from a solid dosage form can be enhanced by addition of suitable disintegrants.

Mechanism of Disintegrants

1) High swellability
2) Capillary action and high swellability
3) Chemical reaction

The most popular disintegrants are corn starch, soluble starch etc. which have been well dried and powdered. Starches have great affinity for water and swell when moistened thus facilitating the rupture of the tablet matrix, its disintegration

action in tablets is due to capillary action. Spherical shape of starch increases the porosity of tablet thus promoting capillary action.

Significance of the Immediate Release tablet

1. Ease of swallowing: Dysphasic population constitute 35% of the general population, since this disorder is associated with a number of medical conditions such as Stroke, Parkinson's disease, AIDS, Head and Neck Radiation Therapy and other neurological disorders.

2. Accurate dose: The immediate/fast dissolve dosage forms have the added advantages of convenience and accurate dosing as compared to liquids.

3 . Rapid drug therapy intervention is possible.

4. New business opportunities like product differentiation, line extension and lifecycle management, exclusively of product promotion.

MATERIALS AND METHODS

Topiramate was gifted by zyduscadilaahmedabad, croscarmellosena from dow chemical company, Microcrystalline Cellulose from FMC Biopolymers, Pregelatinised Starchfrom colorcon ,Povidone K 30 from ISP Technology,Dicalcium Phosphate Anhydrous fromDMV International, Colloidal Silicon Dioxidefrom Evonik/Degussa,Magnesium stearate from Ferro BEOpadry white from Colorconreceived as gift samples and all other chemicals and reagents were of analytical grade.

METHOD FOR PREPARATION OF IMMEDIATE RELEASE TABLET OF TOPIRAMATE

Immediate release tablets were prepared by wet granulation method. The step wise processes were given below.

1. **Dispensing:**Accurately weigh and dispense separately each excipient.
2. **Sifting:**Sift the API and other intragranular excipients by sieve # 30 ASTM and collect in duly labelled polyethylene lined container.
3. **Dry Mixing:**Manually load sifted intra-granular materials in Rapid Mixer Granulation **(**RMG) and mix at slow/off for 5 minutes.
4. **Wet granulation method:** Add purified water slowly in the Rapid Mixer Granulator. The parameters of Rapid Mixer Granulator are in following table:
5. **Drying of granules:**Granules were dried in fluidized bed dryer at 60°C ± 7°C inlet temperature and dried for the period of 40 minutes till the loss on drying (LOD) was between 1.0 to 2.0 %.
6. **Sizing of Granules:**Size the dried granules of using an Oscillating Granulator through 0.8 mm stainless steel screen. Collect the granules into the clean double lined polybag.
7. **Blending and Lubrication:**Sift other extra granular materials by sieve # 40 ASTM and crosscarmellose sodium, colloidal silicon dioxide through sieve no 40 # ASTM and collect in duly labeled polyethylene lined container. Mix the sifted material except magnesium stearateand in a blender for 5 min. Lubricate by magnesium stearate and for 5 min. Record the Loss on Drying.
8. **Compression:**Compression parameters were set according to the shape and size of punches. Compression was performed on the Single rotary machine of 16 stations. Hardness of the tablet would be set as much as capable to withstand the transportation after packaging.

Evaluation parameters 0f topiramate Immediate release tablet

1. Weight Variation[(5)]: Ten tablets were selected randomly from each formulation and weighed individually to check for weight variation. The US Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed:

In all formulations, the tablets weight 307.5 mg ± 7.5% (284.5 – 330.5 mg) are allowed.

2. Hardness[(5)]:10 Tablets from each batch were taken and their hardness was measured using ERWEKA Hardness tester and reported.

3. Thickness[(5)]:10 tablets from each batch were taken and their thickness was measured using ERWEKA tester and reported.

4. Diameter[(5)]:10 tablets from each batch were taken and their diameter was measured using ERWEKA tester and reported.

5. Friability test[(5)]: Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the Purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the

tablets at a distance of 6 inches with each revolution. Preweighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weight.

6. Assay: One tablet was weighed and powdered. The whole amount of powdered tablet was transferred into a 500 ml volumetric flask. Add 300 ml of diluent and sonicate at 25°C for about 30 minutes, make up the volume with diluent. Filter the solution through 0.45 µm Nylon filter after discarding about 2 ml of the filtrate. The concentration of Api(in µg/ml) was calculated by using the standard calibration curve ofAPI.

Drug content in mg was calculated by using formula:

$$\frac{\text{Area of sample x standard wt. x 5 x average wt(mg)}}{\text{Area of standard x 100x sample wt. x label claim(mg)}} \times \%\ \text{potency of std.}$$

Drug content claim was 100mg per tablet. This procedure was followed for 5 tablets from each formulation. The mean and standard deviation values were also calculated.

7.Bulk Density[4]: An accurately weighed quantity of powder, which was previously passed through sieve # 40 [USP] and carefully poured into graduated cylinder. Then after pouring the powder into the graduated cylinder the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as ml. The volume measure was called as the bulk volume and the bulk density is calculated by following formula**:**

$$\text{Bulk Density} = \frac{\text{Weight of powder}}{\text{Bulk volume}}$$

8. Tapped Density[4]: After measuring the bulk volume the same measuring cylinder was set into tap density apparatus. The tap density apparatus was set to 300 taps drop per minute and operated for 500 taps. Volume was noted as (Va) and again tapped for 750 times and volume was noted as (Vb). If the difference between Va and Vb not greater than 2% then Vb is consider as final tapped volume. The tapped density is calculated by the following Formula:

$$\text{Tapped Density} = \frac{\text{Weight of powder}}{\text{Tapped volume}}$$

9. Compressibility Index and Hausner's Ratio[4]: In recent years compressibility index (C.I.) and the closely related Hausner ratio have become the simplest, fastest and the most popular methods for predicting powder flow characteristics. The (C.I.) has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials since all these can influence the observed compressibility index. The C.I. and Hausner ratio are determined by measuring both the bulk volume and the tapped volume of a powder.

$$\text{Compressibility index} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} \times 100$$

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

10.*In–Vitro* Disintegration time[5]:The disintegration time of tablet was measured in water (37°C) according to USP disintegration test apparatus. Three trials for each were performed.

11. *In-Vitro* Dissolution Study of Tablets:The dissolution test was carried out using the standard USP Type II (Paddle apparatus) Electrolab Dissolution Apparatus.

Medium : WATER
Volume : 900 ml
Apparatus :USP-II (paddle)
Stirrer Speed : 50 RPM
Temperature : 37° C ± 0.5° C
Sampling time : 10, 20, 30, 45 and 60 min.
Sampling Volume : 10 ml
Detection : UV-Vis Spectrophotometry

RESULTS AND DISSCUSSION:

- Preformulation studies of were performed; the FTIR analysis revealed that the superdisintegrant and excipients used were compatible with API.
- Immediate release tablets of API can be prepared by Wet granulation technique using the superdisintegrant, namely Croscarmellose Sodium, MCC as Adsorbant, Povidone k30 as binder, Dicalcium phosphate Anhydrous as diluent, Colloidal silicon dioxide as glidant and Magnesium stearate as lubricant.
- Among all the formulations, F8 formulation was finally optimized. It is fulfilling all the parameters satisfactorily. It has shown excellent thickness, hardness, in vitro disintegration and in vitro dissolution.
- Overall, optimization was carried out for the formulation F10 and F11 for sizing; formulation F12 and F13 for lubrication time and formulation F14, F15 and F16 for kneading time.
- The formulation F8 was selected for stability studies on the basis of its better and satisfactory evaluation study

parameters. This formulation showed not much

- Variation in any parameter even after the period of 3 formulations F8 was found to be stable and retained its original properties.
- Also, the formulation F8 was compared with marketed formulation and this formulation showed not much months. From these results it was concluded that, variation in *In-vitro* dissolution release study of the drug.

The values of pre and postcompression parameters evaluated were within prescribed limits and indicated a good free flowing property. Precompression parameters are shown in **Table.3**. The post compression parameters such as hardness, weight variation, thickness, disintegration time, assay, are shown in **Table 4.**

TABLES AND FIGURES:

Table 1: composition of trials for batches f1-f8

Ingredients	**Quantity(mg/tab)**							
Batch No.	**F-01**	**F-02**	**F-03**	**F-04**	**F-05**	**F-06**	**F-07**	**F-08**
	Intra-Granular							
API	100	100	100	100	100	100	100	100
Dicalcium phosphate anhydrous	72	77	74	80	72	62	59	62
MCC (Comprecel M102)	100	100	100	87	100	100	100	100
CrosCarmellose Sodium				5		5	10	10
Povidone k 30	10	10	10	10	10	15	10	10
P.Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	Extra -granular							
Croscarmellose Sodium.		5	8	10	10	10	10	10
Pregelatinised starch	10							
Colloidal silicon dioxide	3	3	3	3	3	3	3	3
Mg. Stearate	5	5	5	5	5	5	8	5
	Film coating							
Opadry white	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
p.water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight of tablet	307.5	307.5	307.5	307.5	307.5	307.5	307.5	307.5

Table 2: composition of trials for batches f9-f16

Ingredients	Quantity(mg/tab)							
Batch No.	F-09	F-10	F-11	F-12	F-13	F-14	F-15	F-16
Intra-Granular								
API	100	100	100	100	100	100	100	100
Dicalcium phosphate anhydrous	64	62	62	62	62	62	62	62
MCC (Comprecel M102)	100	100	100	100	100	100	100	100
CrosCarmellose Sodium	12.5	10	10	10	10	10	10	10
Povidone k 30	5.5	10	10	10	10	10	10	10
P.Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Extra –granular								
Croscarmellose Sodium.	10	10	10	10	10	10	10	10
Pregelatinised starch								
Colloidal silicon dioxide	3	3	3	3	3	3	3	3
Mg. Stearate	5	5	5	5	5	5	5	5
Film coating								
Opadry white	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
p.water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight of tablet	307.5	307.5	307.5	307.5	307.5	307.5	307.5	307.5

Table-3: Precompressional Parameters of topiramate immediate release tablet:

Formulation Code	B.D. (gm/ml)	T.D. (gm/ml)	C. I. (%)	Hausner ratio	Angle of Repose (degrees)
F1	0.424 ± 0.001	0.517 ± 0.01	18.00 ± 0.01	1.21 ± 0.01	39.90 ± 0.01
F2	0.412 ±0.015	0.530 ±0.021	22.23 ± 0.01	1.29 ± 0.01	40.13 ± 0.01
F3	0.348 ±0.001	0.401 ± 0.001	13.22 ± 0.01	1.15 ± 0.01	19.98 ± 0.01
F4	0.523 ± 0.002	0.604 ± 0.017	13.41 ± 0.02	1.15 ± 0.01	20.36 ± 0.015
F5	0.382 ± 0.001	0.439 ± 0.002	12.98 ± 0.01	1.15 ± 0.01	20.60 ± 0.015
F6	0.421 ± 0.002	0.492 ± 0.002	14.43 ± 0.02	1.17 ± 0.02	21.41 ± 0.01
F7	0.465 ± 0.015	0.532 ± 0.001	12.59 ± 0.01	1.14 ± 0.01	20.16 ± 0.015
F8	0.332 ± 0.002	0.375 ± 0.015	11.46 ± 0.01	1.13 ± 0.01	19.66 ± 0.02
F9	0.345 ± 0.018	0.401 ± 0.012	13.97 ± 0.01	1.16 ± 0.02	24.72 ± 0.01
F10	0.386 ± 0.002	0.443 ± 0.015	12.87 ± 0.01	1.15 ± 0.01	22.31 ± 0.015
F11	0.373 ± 0.012	0.446 ± 0.03	16.67 ± 0.01	1.20 ± 0.01	25.12 ± 0.015
F12	0.409 ± 0.001	0.462 ± 0.001	11.47 ± 0.01	1.13 ± 0.01	23.26 ± 0.001
F13	0.368 ± 0.003	0.429 ± 0.001	14.22 ± 0.01	1.17 ± 0.01	27.65 ± 0.023
F14	0.425 ± 0.015	0.491 ± 0.002	13.44 ± 0.01	1.16 ± 0.02	25.98 ± 0.001
F15	0.383 ± 0.012	0.456 ± 0.03	16.01 ± 0.01	1.19 ± 0.02	24.12 ± 0.036
F16	0.419 ± 0.001	0.472 ± 0.01	11.23 ± 0.01	1.12 ± 0.01	22.24 ± 0.002

Table-4: Post compressional Parameters of topiramate immediate release tablets:

Formulation Code	Weight Variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Disintegration Time (min)	Assay (%)
F1	292.12 ± 2.22	4.84 ± 0.87	4.75 ± 0.17	4.54 ± 1.03	96.26
F2	296.06 ± 1.63	4.91 ± 0.94	4.68 ± 0.25	3.32 ± 1.02	97.95
F3	297.16 ± 1.58	4.61 ± 0.12	4.83 ± 0.95	2.51 ± 0.65	99.62
F4	303.52 ± 1.03	4.50 ± 0.02	5.07 ± 0.87	2.10 ± 0.74	99.84
F5	304.18 ± 2.39	4.65 ± 0.23	5.00 ± 0.18	2.12 ± 0.35	101.10
F6	302.08 ± 1.16	4.80 ± 0.04	4.77 ± 0.12	1.80 ± 0.54	99.86
F7	306.44 ± 0.85	4.51 ± 0.08	4.92 ± 0.21	1.70 ± 0.56	100.02
F8	301.06 ± 0.39	4.59 ± 0.26	5.02 ± 0.18	1.42 ± 0.84	101.20
F9	299.41 ± 2.21	4.82 ± 0.02	4.77 ± 0.23	1.20 ± 0.44	101.25
F10	302.28 ± 1.30	4.55 ± 0.03	4.95 ± 0.72	1.45 ± 0.77	101.04
F11	304.84 ± 1.51	4.51 ± 0.02	4.90 ± 0.62	1.50 ± 0.68	102.63
F12	306.70 ± 0.87	4.60 ± 0.03	5.03 ± 0.32	1.40 ± 0.34	102.11
F13	304.56 ± 1.53	4.92 ± 0.08	4.60 ± 0.22	1.52 ± 0.42	100.52
F14	302.38 ± 0.49	4.60 ± 0.08	4.84 ± 0.42	1.60 ± 0.22	102.38
F15	302.20 ± 1.56	4.58 ± 0.04	5.04 ± 0.36	1.48 ± 0.64	101.42
F16	304.34 ± 2.38	4.60 ± 0.06	5.02± 0.88	1.40 ± 0.36	102.28

Table5: *In Vitro* release study for batches f1-f3

% CUMULATIVE DRUG RELEASED			
Time (minutes)	**F1**	**F2**	**F3**
0	0	0	0
10	30.2 ± 1.91	48.5 ± 5.35	62.5 ± 1.48
20	49.5 ± 2.90	67.2 ± 2.33	78.6 ± 0.87
30	63.7 ± 2.56	78.3 ± 1.88	89.8 ± 0.43
45	78.1 ± 2.23	89.1 ± 0.69	94.1 ± 1.06
60	90.2 ±1.63	97.4 ± 0.15	97.9 ± 0.91

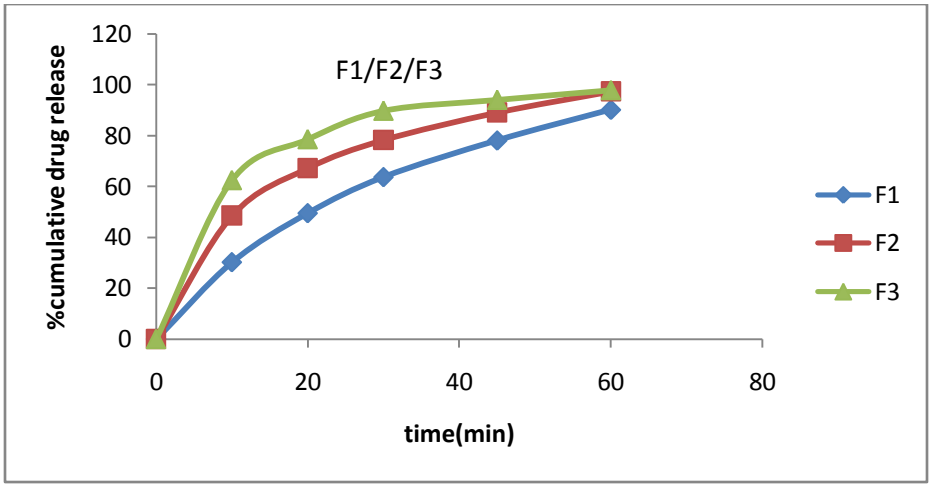

Figure-1: *in vitro* release profile of f1,f2,f3

Table-6: *In Vitro* release study for batches f4-f6

% CUMULATIVE DRUG RELEASED			
Time (minutes)	**F4**	**F5**	**F6**
0	0	0	0
10	64.7 ± 2.91	68.2 ± 1.35	61.8 ± 1.24
20	78.8 ± 1.90	88.2 ± 1.33	83.2 ± 1.77
30	90.6 ± 3.56	97.7 ± 2.88	94.5 ± 0.14
45	94.8 ± 1.23	98.1 ± 1.12	95.4 ± 2.08
60	98.1 ±1.46	99.5 ± 0.78	98.5 ± 1.82

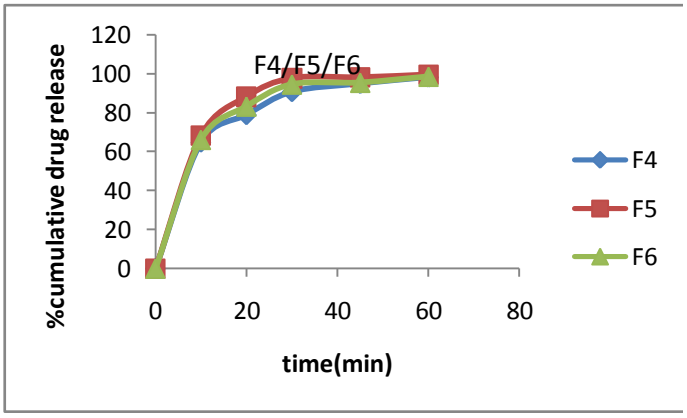

Figure-2: *in vitro* release profile of f4,f5,f6

Table-7: *In Vitro* release study for batches f7-f9

% CUMULATIVE DRUG RELEASED			
Time (minutes)	**F7**	**F8**	**F9**
0	0	0	0
10	60.1 ± 0.22	87.1 ± 1.48	85.7 ± 1.36
20	79.8 ± 2.40	95.8 ± 1.26	94.8 ± 2.18
30	90.4 ± 2.26	98.6 ± 0.78	98.2 ± 0.44
45	93.3 ± 1.43	99.2 ± 1.52	98.9 ± 2.06
60	97.8 ± 0.46	99.8 ± 0.20	99.2 ± 1.60

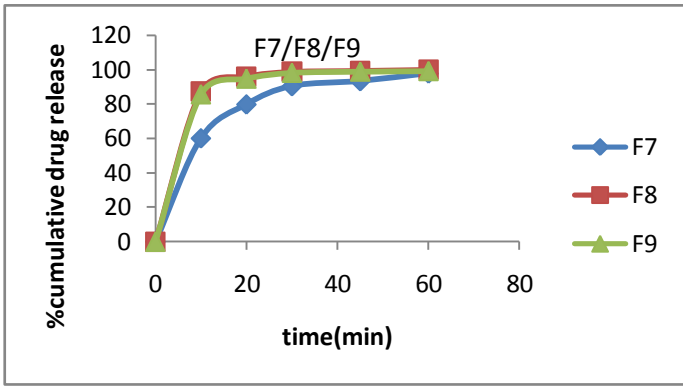

Figure 3:*in vitro* release profile of f7,f8,f9

Table-8: *In Vitro* release study for batches f8,f10,f11

% CUMULATIVE DRUG RELEASED			
Remarks	**Sized with 0.8 mm ss screen**	**Sized with 0.5 mm ss screen**	**Sized with 1.2 mm ss screen**
Time (minutes)	**F8**	**F10**	**F11**
0	0	0	0
10	87.1 ± 1.48	85.3 ± 3.74	86.1 ± 0.95
20	95.8 ± 1.26	92.4 ± 3.01	93.7 ± 0.78
30	98.6 ± 0.78	96.1 ± 2.85	96.9 ± 0.81
45	99.2 ± 1.52	98.3 ± 2.63	98.7 ± 0.55
60	99.8 ± 0.20	99.2 ± 0.66	99.6 ± 0.42

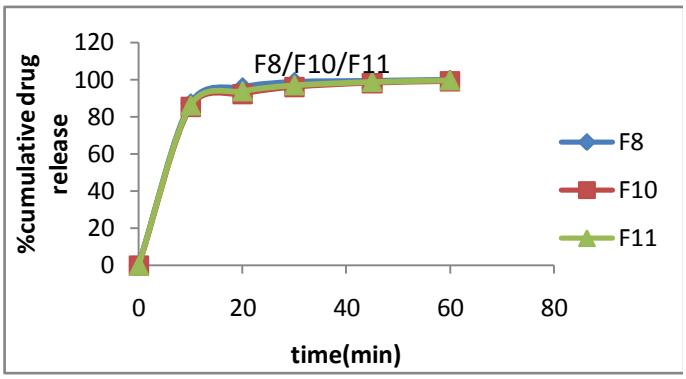

Figure-4: *in vitro* release profile of batchesf8,f10,f11

Table-9: *In Vitro* release study for batches f8,f12,f13

% CUMULATIVE DRUG RELEASED			
Remarks	**Lubrication time for 5 min.**	**Lubrication time for 2 min.**	**Lubrication time for 10 min.**
Time (minutes)	**F8**	**F12**	**F13**
0	0	0	0
10	87.1 ± 1.48	84.3 ± 1.03	82.1 ± 0.84
20	95.8 ± 1.26	93.4 ± 0.48	91.6 ± 0.92
30	98.6 ± 0.78	96.1 ± 0.96	97.5 ± 0.95
45	99.2 ± 1.52	98.2 ± 0.13	97.9 ± 1.10
60	99.8 ± 0.20	99.1 ± 1.05	98.9 ± 0.81

Table 10: *In – Vitro* release study for batches f8,f14,f15,f16

% CUMULATIVE DRUG RELEASED								
Remarks	**Optimum Kneading (60 second)**	**Low Kneading (30 second)**		**High Kneading (90 second)**		**Highest Kneading (120 second)**		
Time (minutes)	**F8**	**F14**		**F15**		**F16**		
0	0	0		0		0		
10	87.1 ± 1.48	86.3	± 2.18	83.1	± 3.03	82.4	± 2.84	
20	95.8 ± 1.26	93.8	± 3.18	92.5	± 4.21	92.1	± 1.99	
30	98.6 ± 0.78	96.4	± 2.13	95.5	± 3.49	94.3	± 2.04	
45	99.2 ± 1.52	98.5	± 1.75	98.1	± 2.92	97.3	± 1.17	
60	99.8 ± 0.20	99.7	± 1.28	99.2	± 2.13	98.9	± 1.32	

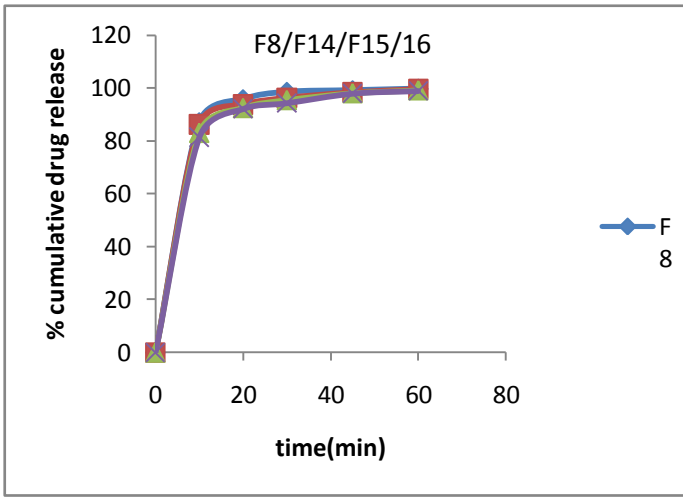

Figure-6: *in vitro* release profile of batches f8,f14,f15,f16

Comparision of Formulation F8 with the Marketed Formulation:

Innovator: Apotex Inc.

Brand name: Topamax 100mg Tablet

Hardness (kg/cm^2): 5.4 ± 9.27

Average weight (mg): 300 ± 2.59

Thickness (mm): 4.6 ± 0.03

The % Cumulative drug released of the formulation F8 and Marketed formulation was shown in table no: 11 and the comparative dissolution graph shown in figure 7.

Table 11: *In Vitro* release study of f8 and marketed formulation

% CUMULATIVE DRUG RELEASED		
Time (minutes)	**F8**	**Marketed Formulation**
0	0	0
10	87.1 ± 1.48	86.2 ± 1.23
20	95.8 ± 1.26	93.7 ± 0.32
30	98.6 ± 0.78	96.8 ± 0.64
45	99.2 ± 1.52	98.4 ± 0.13
60	99.8 ± 0.20	99.2 ± 0.05

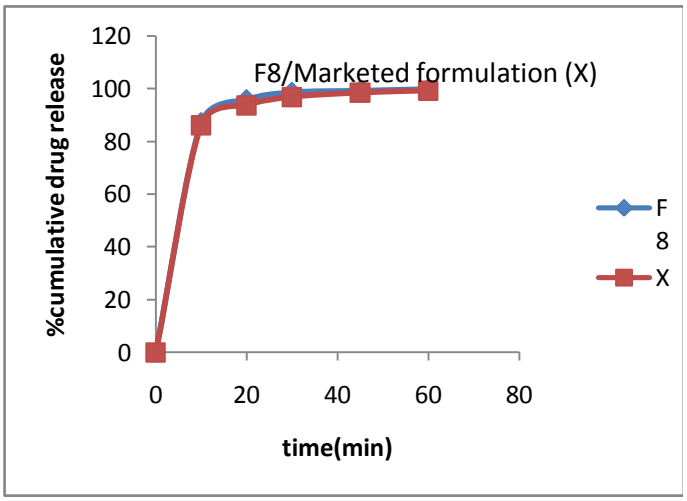

Figure-7: *in vitro* release profile of batches f8,f14,f15,f16

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