

Research Article



Formulation and Evaluation of Immediate Release Tablets of Topiramate Using Croscarmellose Sodium

Kanhu Charan Panda¹, Chinmaya Keshari Sahoo², Jimidi Bhaskar³, Ch.Swati³, T.Madhuri, D. Venkata Ramana⁴

¹Department of Pharmaceutics, Anwar-ul-Uloom College of Pharmacy, Ranga Reddy, Telangana, India.

²Department of Pharmaceutics, Malla Reddy College of Pharmacy (Affiliated to Osmania University), Maisammaguda, Hyderabad, Telangana, India.

³Department of Pharmacy, Avanthi Institute of Pharmaceutical Sciences, Gunthapally (V), Near Ramoji Film City, Hyderabad, Telangana-501505.

⁴Department of pharmaceutical Technology, Netaji Institute of Pharmaceutical Sciences, Toopranpet, Yadadri Bhongir, Telangana, India.

*Corresponding author's E-mail: sahoo.chinmaya83@gmail.com

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ABSTRACT

The objective of the present study was to develop immediate release tablets (IRT) of topiramate using different concentrations of croscarmellose sodium (CCS) as superdisintegrant for the treatment of epilepsy. Four different formulations of IRT were prepared using wet granulation method. Different pre compression and post compression characterization of tablet was carried out. In vitro drug release studies were carried out in USP II paddle type dissolution apparatus for different formulation and the batch containing 7.5 mg of CCS per tablet gave maximum amount of drug release of 93.96% at the end of 50 mins. Drug and excipients compatibility studies were carried out through FTIR spectroscopy. FTIR spectroscopy studies revealed that there is no interaction between drug and different excipients used in formulation. Short term stability studies (at 40±2°C/75±5% RH) on the best formulation indicated that there was no significant change in release profile and drug content after a period of one to three month. Among all the formulations, F4 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: IRT, topiramate, CCS, in vitro drug release study, FTIR spectroscopy.

INTRODUCTION

The oral route¹ of drug administration is one of the popular routes of drug administration. The tablets are still the most commonly used dosage forms due to its continuous development and implementation of innovative ideas to overcome the basic shortcomings of the existing formulations. The advances in drug delivery systems for designing dosage forms like IRTs for convenient to be manufactured and administered free side effects, and enhance bioavailability² so as to achieve better patient compliance. IRT are most commonly formulated when rapid response is required. Super disintegrant is the vital component along with various common excipients like diluents, binder, lubricants, glidant etc used for the preparation of IRT. Immediate release drug delivery³ is desirable for drugs having long biological half life, high bioavailability, lower clearance and lower elimination half life. For IRT the drug is intended to be released rapidly after administration, or the tablet is dissolved and administered as a solution. IRT tablets are those tablets which are designed to disintegrate⁴ and release their medication.

Topiramate⁵ is a sulfamate substituted monosaccharide has been approved for use as an antiepileptic agent, as an adjuvant therapy for patients with partial onset seizures or primary generalized tonic-clonic seizures, and for the prevention of migraine. Topiramate blocks voltage-dependent sodium channels, augments the activity of the neurotransmitter gamma amino butyrate at some subtypes of the GABA-A receptor. Absorption of Topiramate is rapid, with peak plasma concentrations

occurring at approximately 2 hours. The relative bioavailability of Topiramate from the tablet formulation is about 80% compared to a solution. The average elimination half-life of Topiramate is approximately 22 hours. In the present study IRT of topiramate were designed using wet granulation method using various excipients and croscarmellose sodium as natural super disintegrants with prime objective arriving of a cost effective product.

MATERIALS AND METHODS

Materials

Topiramate was gifted by Zydus Cadila, Ahmedabad, and croscarmellose sodium from Dow chemical company. Magnesium stearate, talc, micro crystalline cellulose (Avicel 101, Avicel 102), and potassium dihydrogen-phosphate were procured from SD fine chem. Ltd Mumbai. Sodium hydroxide and CCS were procured from Qualigens fine chemicals Mumbai.

Drug excipient studies

Fourier Transform Infrared Spectroscopy (FTIR)

In this method individual samples as well as the mixture of drug and excipients were ground mixed thoroughly with potassium bromide (1:100) for 3-5 mins in a mortar and compressed into disc by applying pressure of 5 tons for 5 mins in hydraulic press. The pellet was kept in the sample holder and scanned from 4000 to 400 cm⁻¹ in FTIR spectrophotometer.



Preparation of IRT

IR tablets each containing 50 mg topiramate were prepared by wet granulation method. The granules of topiramate were prepared by sieving Avicel pH 101, Avicel pH 102, cross carmellose sodium, pre gelatinized starch through sieve no 80. The diluents (Avicel PH 101 and 102), half of the quantity of super disintegrant (cross carmellose) and drug were taken in a motor and pestle and trituration was done for 5 mins. Binding solution was prepared by taking binders pre gelatinized starch and dissolve in required volume of solvent. Wet or dough mass was prepared by mixing of binder solution with the above triturated mixture for 10 mins and passed through sieve no 10 to obtain wet granules. The wet granules were dried at 60°C for 15 mins, and then dried granules were passed through sieve no 20 to break the aggregates. Then remaining half quantity of super disintegrant, Magnesium stearate and talc were passed through sieve no 80, added to the dried granule and blended for 3 mins. The prepared granules were subjected for compression using embossed flat punch (10 station rotary tablet machine, Clint India).

Table 1: Composition of topiramate IRT

Ingredients(mg)	F1	F2	F3	F4
Topiramate	50	50	50	50
Avicel 101	72	69.5	64.5	74.5
Avicel 102	65	65	60	40
Pregelatinized Starch	10	10	15	20
Crosscarmellose sodium(CCS)	0	2.5	5	7.5
Magnesium Stearate	2	2	2	2
Talc	1	1	1	1
Total weight(mg)	200	200	200	200

Evaluation of granules

Pre compression parameters of IRT

Angle of repose

The angle of repose⁶ of granules blend was determined by the fixed funnel method. The accurately weighed quantity of granules was taken in a funnel. The height⁷ of funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules are allowed to flow through the funnel freely onto the surface. The diameter of powder cone was measured and angle of repose was calculated using the following equations

$$\tan\theta = h/r \dots\dots\dots (1)$$

$$\theta = \tan^{-1}(h/r) \dots\dots\dots (2)$$

Where θ is the angle of repose, h is the height of cone in cm and r is the radius of the cone base in cm.

Bulk density (e_b)

Bulk density⁷ was determined by pouring the granules into a graduated cylinder in bulk density apparatus (Sisco, India). The bulk volume (V_b) and mass (m) of the granules was determined. The bulk density was calculated by using the following formula.

$$e_b = m/V_b \dots\dots\dots (3)$$

Tapped density (e_t)

The measuring cylinder containing known mass of granules blend was tapped 1000 times for a fixed time in bulk density apparatus (Sisco, India). The minimum volume occupied in the cylinder (V_t) and mass of the granules (m) was measured. The tapped density was measured by using the following formula.

$$e_t = m/V_t \dots\dots\dots (4)$$

Compressibility index (Carr's index)

The compressibility index determines the flow property characteristics of granules developed by Carr. The percentage compressibility of granules is a direct measure⁸ of the potential powder arch and stability. The Carr's index can be calculated by the following formula.

$$\% \text{Carr's index} = e_t - e_b / e_t \times 100 \dots\dots\dots (5)$$

Where e_t is the tapped density of granules and e_b is bulk density of granules

Hausner's ratio

Hausner's ratio is used for the determination of flow properties of granules. The ratio can be calculated by the taking the ratio of tapped density to the ratio of bulk density.

Post compression parameters of IRT

Thickness

The thickness⁹ of individual tablets are measured by using vernier caliper. Generally the unit for thickness measurement is mm. The limit of the thickness deviation of each tablet is $\pm 5\%$.

Hardness

The hardness¹⁰ of a tablet is associated with the resistance of the solid specimen towards fracturing and attrition. The hardness of tablets can be determined by using Monsanto hardness tester and measured in terms of kg/cm^2 .

Friability

Friability¹¹ of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at the height of 6 inches in each revolution. Pre weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted



using soft muslin cloth and reweighed. The %friability (%) is given by the formula.

$$\%F = \frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}} \times 100 \dots \dots \dots (6)$$

Where, W_{initial} and W_{final} are the weight of the tablets before (initially weight) and after (final weight) the test respectively.

Weight Variation

The weight variation test was done by weighing 20 tablets individually (Shimadzu digital balance), calculating the average weight and comparing the individual tablet weights to the average. The percentage weight deviation was calculated and then compared with USP specifications.

Disintegration test

The disintegration time¹² was measured using disintegration test apparatus. One tablet was placed in each tube of the basket. The basket with the bottom surface made of a stainless-steel screen (mesh no.10) was immersed in water bath at $37 \pm 0.5^\circ\text{C}$. The time required for complete disintegration of the tablet in each tube was determined using a stop watch. To be complied with the pharmacological standards, dispersible tablets must disintegrate within 3min when examined by the disintegration test for tablets.

Drug Content

Three tablets from each formulation batch were powdered and a quantity equivalent to 5 mg of topiramate was transferred to 100 ml of volumetric flask and diluted to 100 ml with methanol.

15 ml of this solution was taken and diluted to 100 ml with methanol and absorbance was measured at 210nm. Concentration of topiramate was determined using calibration curve of topiramate in methanol.

In vitro dissolution studies

In vitro dissolution studies¹³ for all the fabricated tablets was carried out using USP paddle method at 100 rpm in 900 ml of HCl buffer pH 1.2 as dissolution media, maintained at $37 \pm 0.5^\circ\text{C}$. 5 ml aliquot was withdrawn at the specified time intervals, filtered through whatman filter paper and then equal volume of fresh medium, which was pre-warmed at 37°C was replaced into the dissolution media after each sampling to maintain the constant volume throughout the test. The samples are then analyzed spectrophotometrically at 210 nm and the absorbance can be known.

Stability studies

The formulation was subjected to accelerated stability studies as per ICH (The International Conference of Harmonization) guidelines. The packed tablets¹⁴ in air tight container were placed in stability chambers (Thermo lab scientific equipment Pvt.Ltd. Mumbai, India) maintained at $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$ for 3 months. Tablets were periodically removed and evaluated for physical characteristics, drug content, *in-vitro* drug release etc.. At intervals of one week, the tablets were visually examined for any physical changes, and changes in drug content.

RESULTS AND DISCUSSION

Drug excipient studies

Fourier Transform Infrared Spectroscopy (FTIR)

From the IR study the major peak of topiramate and optimized formulation were found to be no interaction between the drug and disintegrant. Hence FTIR study showed that drug and excipients were compatible.

Pre-compression parameters of granules

The granules were evaluated for pre-compression parameters such as angle of repose bulk density, tapped density, Carr's index and Hausner's ratio. All the evaluated precompression parameter values were within acceptable range of pharmacopoeial limits. It is reported in table 2.

Table 2: Pre-compression parameters of IR formulations

Formulation code	Angle of repose (degree) ^a ± S.D	Bulk density (gm/ml) ^a ± S.D	Tapped density (gm/ml) ^a ± S.D	Carr's Index (%) ^a ± S.D	Hausner's Ratio ^a ± S.D
F1	29.65 ± 0.13	0.468 ± 0.03	0.533 ± 0.02	12.19 ± 0.06	1.13 ± 0.03
F2	26.73 ± 0.12	0.483 ± 0.11	0.536 ± 0.09	9.88 ± 0.06	1.10 ± 0.08
F3	26.52 ± 0.08	0.477 ± 0.01	0.534 ± 0.03	10.67 ± 0.04	1.11 ± 0.06
F4	25.63 ± 0.11	0.481 ± 0.04	0.529 ± 0.05	9.07 ± 0.05	1.09 ± 0.04

N.B. All values are expressed as mean ± S.D, ^a n = 3.

Post-compression parameters of IR formulations

The post compression parameters such as thickness, hardness, friability, weight variation, disintegration time, and drug content were evaluated. All the evaluated

postcompression parameter values were within acceptable range of pharmacopoeial limits. It is reported in table 3.



Table 3: Post-compression parameters of IR formulations

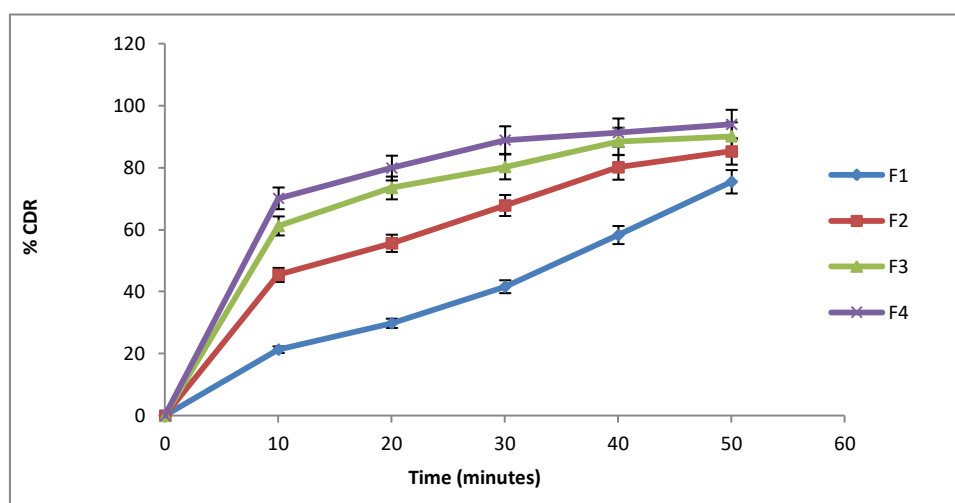
Formulation code	Thickness (mm) ^a ± S.D	Hardness (kg/cm ²) ^a ± S.D	%Friability (%) ^b ± S.D	Average weight of tablet(mg) ^a ± S.D	Disintegration time(min.) ^c ± S.D	%Drug content ^a ± S.D
F1	3.51 ± 0.01	4.8 ± 0.12	0.71 ± 0.03	200.18 ± 1.16	4.1 ± 0.03	97.92 ± 1.32
F2	3.52 ± 0.02	4.9 ± 0.11	0.76 ± 0.02	200.4 ± 1.03	3.8 ± 0.11	99.32 ± 1.41
F3	3.49 ± 0.03	4.4 ± 0.16	0.74 ± 0.03	200.3 ± 1.02	3.6 ± 0.15	98.64 ± 0.98
F4	3.5 ± 0.01	4.1 ± 0.18	0.80 ± 0.02	200.12 ± 1.06	2.9 ± 0.12	98.96 ± 1.4

N.B. All values are expressed as mean ± S.D, ^a n = 10, ^b n = 20, ^c n = 3

In vitro drug release study:

The % cumulative drug release (CDR) of various batches were F1 (75.44%), F2 (85.22%), F3 (90.11), and F4 (93.96) respectively at the end of 50 mins. The dissolution

profiles of prepared batches of topiramate F1-F4 were shown in figure 1. Among all the formulations F4 showed maximum percentage of CDR due to higher concentration of CCS.

**Figure 1:** Comparative *in vitro* drug release profiles of formulations F1-F4

Short-term stability studies

Short-term stability studies on the above promising formulation (at 40±2° / 75±5% RH for 3 months) have shown no significant changes in physical appearance,

drug content. There were no appreciable changes *in vitro* drug release up on storage at 40 ± 2°/75 ± 5% RH for 3 months period.

Table 4: Stability study of optimized formulation (F4)

Parameters	After 30 days	After 60 days	After 90 days
Physical appearance	No change	No change	No change
Weight variation(mg) ^b ± S.D	200.12 ± 1.06	200.10 ± 1.06	200.10 ± 1.06
Thickness(mm) ^a ± S.D	3.5 ± 0.01	3.51 ± 0.01	3.52 ± 0.01
Hardness(kg/cm ²) ^a ± S.D	4.1 ± 0.18	4.0 ± 0.11	4.0 ± 0.15
Friability(%) ^b ± S.D	0.80 ± 0.02	0.85 ± 0.07	0.88 ± 0.06
Drug content(%) ^a ± S.D	98.96 ± 1.4	98.96 ± 1.4	97.92 ± 1.8

N.B.-All values are expressed as mean ± S.D, ^a n = 10, ^b n = 20

CONCLUSION

From the study it can be concluded that immediate release tablets of topiramate could be successfully prepared by wet granulation method in a cost effective manner employing CCS as superdisintegrant. The drug release of topiramate is best in F4 from *in vitro* drug

release study as it contains highest concentration (7.5 mg) of CCS per tablet. From the stability study of the formulation carried out by storing at 40±2°C / 75±5% RH for 3 months showed that there was no significant change in drug content and percentage drug release. It proved that the product is stable.



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