The history of a drug manufacturer biology essay

Science, Biology

Name: Topiramate Gifted from Cadila Healthcare Ltd., Ahmedabad.

B. Excipients

β cyclodextrin Chemodyes corp, RajkotMicrocrystalline cellulose Chemodyes corp, RajkotAvicel Chemodyes corp, RajkotCrospovidone Chemodyes corp, RajkotMannitol Triveni Chemicals, vapiSodium sachharin Triveni Chemicals, vapiSucralose Chemodyes corp, RajkotTalc Chemodyes corp, RajkotMagnesium Stearate Chemodyes corp, RajkotPre gelatinized starch Chemodyes corp, Rajkot

C. Equipments

Electronic balance Shimadzu, JapanTablet compression machine Rimek, minipress 10 station rotarymachine, Karnavathi engineeringltd, Gujarat. Hardness tester Monsanto hardness testerFriability Test Apparatus Roche friability testing apparatusUV visible spectrophotometer UV-1800 Shimadzu corporation, Japan. DSC DSC60 Shimadzu Corporation, Japan. Tablet Dissolution Test Apparatus Electrolab USP (XXIII)

4. 2 Analytical Method38

As per Research Article, Analytical method were carried out using Colorimetric Method.

4. 2. 1 Preparation of Reagents and Buffer

a. Solution of Ammonium Molybdate (5%). The solution of Ammonium molybdate was prepared by dissolving 5 gms of Ammonium molybdate in 100 mlof dist. water. b. 2M hydrochloric acid: 17. 2ml conc. Hcl + 100ml distil waterc. Phosphate buffer (pH 6. 8) solution: 50 ml of 0. 2 M potassium

dihydrogen orthophosphate solution was taken in a 200 ml volumetric flask, to which 22. 4 ml of 0. 2 M sodium hydroxide solution was added. Then volume was made up to the mark with distilled water and pH was adjusted to 6. 8 with dilute sodium hydroxide solution. d. Preparation of Topiramate standard stock solution in phosphate buffer (pH 6. 8) solutionA standard stock solution of Topiramate was prepared by dissolving accurately weighed 10 mg of Topiramate in phosphate buffer (pH 6. 8) solution in a 100 ml volumetric flask and the volume was made up to 100 ml by using phosphate buffer (pH 6. 8) solution to obtain a stock solution of 100 µg/ml.

4. 2. 2 Calibration curve of Topiramate in phosphate buffer (pH 6. 8) solution

From the working standard drug solution of 1, 2, 3, 4, 5, 6 ml (which gives 10-60µg/ml) drug solution was placed in 6 different 10 ml volumetric flasks. Into this 2 ml of 5% of ammonium molybdate was added followed by 2 ml of 2M hydrochloric acid and then volume was made up to 10ml with phosphate buffer 6. 8 and then reaction mixture was kept in water bath for 35 min for the completion of reaction for full color development and the absorbance was measured against a reagent blank. . The absorbencies of these drug solutions were estimated ʎmax 750 nm. This procedure was performed in triplicate to validate the calibration curve. The data and calibration curve are given in the chapter- result and discussion.

4. 3 Preformulation Studies39

The following preformulation studies are performed for Topiramate and polymers: 1. Determination of melting point of Topiramate. 2. Drug–excipient compatibility studies1.) Determination of melting point: Melting point of pure

Topiramate was determined by open capillary method. The capillary tube was closed at one end by fusion and filled with Topiramate by repeated tapings. The capillary tube was place in a digital melting point apparatus. The instrument was set to automatically increase the temperature of the heating bath at a rate of 1 °C rise of temperature per minute. The rise in temperature was determined through magnifying lens. The temperature at which the drug starts melting was recorded. This procedure was performed thrice and the average value was calculated. 2.) Drug–excipient compatibility studies: In the preparation of tablets formulation, drug and excipient may interact as they are in close contact with each other, which could lead to the instability of drug. The drug-excipient interaction are therefore very critical in selecting appropriate excipient. FT-IR spectroscopy was employed to ascertain the compatibility between Topiramate and the selected excipient. Potassium bromide, pure drug, and the Disintegrants were heated to 105o C for one hour to remove the moisture content if present in a hot air oven. Then in presence of IR lamp, potassium bromide was mixed with drug and/or Disintegrants in 9: 1 ratio and the spectra were taken. FT-IR spectrum of Topiramate was compared with FT-IR spectra of Topiramate with Disintegrants. Disappearance and shifting of peaks were observed.

4. 4 Physical properties of bulk and granules

a. Angle of Repose39

Flow properties of the granules were evaluated by determine the angle of repose and the compressibility index. Static angle of repose was measured according to the fixed funnel and free standing cone method of Banker and Anderson. A funnel with the end of the stem cut perpendicular to the axis of

symmetry is secured with its tip at a given height (1cm), h, above graph paper placed on a flat horizontal surface. The granules were carefully poured through the funnel until the apex of the conical pile so formed just reached the tip of the funnel. Thus, with R being the radius of the base of the granules conical pile and angle of reposewas calculated by using the equation. tan ʘ = h / rʘ = tan-1 (h/r)Where, ʘ is the angle of reposeh is height of piler is radius of the base of pileFlow properties for different values of angle of repose are given in Table 4. 1

Table 4. 1: Relationship between angle of repose and flow property

Sr. NO.	ANGLE OF REPOSE	FLOW
1	<25	Excellent
2	25-30	Good
3	30-40	Moderate
4	> 40	Poor

b. Bulk density39

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A suitable amount of powder from each formulation, previously lightly shaken to break agglomerates formed, was introduce into a 10 ml measuring cylinder. After initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from a height of 2. 5cm at 2 seconds intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using following formula. LBD = ...(a)TBD = ...(b)

c. Compressibility index39

Compressibility index of the powder was determined by Carr's compressibility index. Carr's Index (%) = x 100 .....(c)

Table 4. 2: Grading of the powders according to Carr's Index.

Consolidation Index (Carr %)

Flow

5 – 15Excellent12 -16Good18 -21Fair23 -35Poor33 – 38Very poor> 40Very very poor

d. Hausner Ratio39

The Hausner ratio of the powder was determined by the following equation. Hausner ratio =

4. 5 Method of Preparation

Direct compression methodThe each tablet containing 25mg of Topiramate was prepared by direct compression method. The super disintegrants were used in different proportions and in different combinations. All ingredient pass through sieve #80. Then at last magnesium stearate was passed through sieve #60. Final blend was mixed in polybag with proper mixing. Blend was compressed in 100 mg tablets by direct compression method using 10 station rotary punching machine (punch : 5mm, round shape).

4. 6 Formulation Development

The Topiramate tablets are available in 25, 50, 100, and 200 mg doses in the market. Dose of 25 mg is selected for the present study. Dose was calculated by considering the molecular weight. The present study was based on formulation and evaluation of Fast Dissolving tablets prepared by direct compression using three different superdisintegrants like sodium starch glycolate, croscarmellose sodium and crospovidone at three different concentration of these superdisintegrants like 2. 5%, 5% and 7. 5%.

4. 6. 1 Preliminary Trial Batch By Direct Compression Method

Topiramate tablets were manufactured for the trail nine batches using the ingredients mentioned in table 4. 3 keeping the total weight (100 mg) of the tablet constant in all the formulations.

Table 4. 3: Trail Batch of Topiramate tablets (Direct compression method)

Ingradients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Topiramate	252525252525252525								
Crospovidone	2. 55. 07. 5								

Sodium starch glycolate

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2. 55. 07. 5

Crosscarmellose sodium

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2. 55. 07. 5

Talk

555555555

Magnesium stearate

222222222

Aspartame

333333333

Microcrystalline cellulose

1515151515151515

D- mannitol

47. 54542. 547. 54542. 547. 54542. 5

TOTAL (mg)

100100100100100100100100

4. 6. 2 Optimization of fast dissolving tablets of Topiramate

For optimization 32 factorial design was employed to study the effect of independent variables (X1) crospovidone and (X2) sodium starch glycolate. All the batches were prepared according to the experimental design.

Table 4. 4: The effect of independent variables

Independent variable

Variable level

Low

Medium

High

Crospovidone2. 55. 07. 5Sodium starch glycolate2. 55. 07. 5

Table 4. 5: 3² Factorial Design (Direct compression)

Sr. No.

Coded Value

Actual Value

Factor 1 conc of crospovodone (gm) (X1)

Factor 2 conc of sodium starch glycolate (gm) (X2)

Factor 1. conc. of crospovidone (mg)

Factor 2. conc. of Sodium starch glycolate (mg)

F1

-1-12. 52. 5

F2

-102. 55. 0

F3

-112. 57. 5

F4

0-15. 02. 5

F5

005. 05. 0

F6

015. 07. 5

F7

1-17. 52. 5

F8

107. 55. 0

F9

117. 57. 5

4. 7 Evaluation of Topiramate Tablets

4. 7. 1 Appearance40

The tablets were checked for presence of cracks, depressions, pinholes, uniformity of the color and the polish of the tablet.

4. 7. 2 Thickness and Dimension41

Tablets of each batch were selected and measured for thickness and diameter using vernier calipers. The extent to which the thickness of each tablet deviated from ± 5% of the standard value was determined.

4. 7. 3 Hardness of the tablets41

Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The degree of hardness varies with the different manufactures and with the different types of tablets. The hardness was tested using Monsanto tester. " Hardness factor", was determined and reported. The force was measured in kilograms per centimeter square.

4. 7. 4 Friability of Tablets41

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This in process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Permitted friability limit is 1. 0 %. Roche friabilator was used to measure the friability of the tablets. Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. It was rotated at a rate of 25 rpm. After 100 rotations (4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively. The percent friability was determined using the following formula;(W1 – W2)Friability = x 100W1where, W1 = weight of the tablet before testW2 = weight of the tablets after test

4. 7. 5 Weight Variation Test41

Twenty tablets were weighed individually and all together. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (±7. 5%). The percent deviation was calculated using the following formula. Individual weight – Average weightPercentage Deviation = x 100Average weightAny variation in the weight of tablet (for any reason) leads to either under medication or over medication. So, every tablet in each batch should have a uniform weight. Deviation within the BP permissible limit of 7. 5% is allowed as the tablet weighs 100 mg. Corrections were made during the compression of tablets to get uniform weight.

Table 4. 6: BP Standards for Percentage Weight Variation

Average weight of tablet

± Percentage deviation

80 mg or less10More than 80 mg but less than 250 mg7. 5250 mg or more5

4. 7. 6 Drug Content Estimation39

Five tablets were selected randomly and average weight was calculated. Tablets were crushed in a mortar and accurately weighed amount of average tablet was taken from the crushed blend. Then, the samples were transferred to 100 ml volumetric flasks and were diluted up to the mark with Water. The content was shaken periodically and kept for one hour to dissolve of drug completely. The mixtures were filtered and appropriate dilutions

were made. The drug content in each tablet was estimated at ⍭max 284 nm against blank reference and reported.

4. 7. 7 In Vitro disintegration time41

The process of breakdown of a tablet into smaller particles is called as disintegration. The in vitro disintegration time of a tablet is determined using disintegration test apparatus as per IP specifications. IP Specifications: Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using pH 6. 8 (Phosphate buffer) maintained at 37🏭±2🏭C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the pH 6. 8 maintained at 37🏭±2🏭C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

4. 7. 8 Wetting Time and Water absorption ratio39

Wetting time of dosage form is related with the contact angle. Wetting time of the Fast dissolving tablets is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablet can be measured using a simple procedure. MethodFive circular tissue papers of 10 cm diameter were placed in a petridish with a 10 cm diameter. Ten ml of water containing eosin, a water soluble dye was added to petridish. A tablet was carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as wetting time. Water absorption ratio (R) was

calculated using the formulaR = 100 x [Wa – Wb] / WbWhere, Wa = weight of tablet after absorptionWb = weight of tablet before absorption

4. 7. 9 In vitro Dispersion time42

The disintegration time for Fast dissolving tablets needs to be modified as disintegration is required without water, thus the test should mimic disintegration in salivary content. For this purpose, a petridish (10 cm diameter) was filled with 9 ml of phosphate buffer solution, pH 6. 8 (which correlates pH of saliva). The tablet was carefully put in the center of petridish and time for the tablet to completely disintegrate into fine particles was noted.

4. 7. 10 In vitro Dissolution Study43

In vitro drug release studies were carried out by using USP XXIII Dissolution Apparatus II (Paddle Type) at 50 rpm. The drug release profile was studied in 900 ml of distilled water maintained at 37 ± 0. 5°C. Aliquots of 5 ml of dissolution medium were withdrawn at specific time intervals (20, 40, 60, 80 and 100 second); the fresh dissolution medium was replaced every time with the same quantity of the sample. The collected samples were analyzed at 284 nm using dissolution medium as blank. The cumulative percentage drug release was calculated.

4. 7. 11 Stability Study of optimized batch39, 42

Stability is defined as the ability of a particular drug or dosage form in a specific container to remain within its physical, chemical, therapeutic, and toxicological specifications. Drug decomposition or degradation occurs during stability, because of chemical alteration of the active ingredients or

due to product instability, lowering the concentration of the drug in the dosage form. The stability of pharmaceutical preparation should be evaluated at room temperature condition and accelerated condition. The optimized formulation of tropisetron HCl tablets was selected for the stability studies. The room temperature condition (25 + 2oC and 65 + 5% RH) and accelerated condition (40 + 2oC and 75 + 5% RH) were selected according to ICH guidelines for period of 1 month. The tablets were evaluated for hardness, drug content, and dissolution study and compared with tablets which were evaluated immediately after manufacturing.