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Formulation and Evaluation Acamprosate Calcium to Improve the Bioavailability and Dissolution Profiles

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Abstract

Acamprosate (APC) is believed to stabilize the chemical balance in the brain by blocking glutaminergic N-methyl-D-aspartate receptors and activating the gamma-aminobutyric acid type A receptors. Acamprosate is a compound with high solubility and low permeability, BCS - Class III, are not considered highly permeable, they may have site-specific absorption, and so there are a greater number of mechanisms through which excipients can affect their absorption. In the current research the active excipients used in formulations have been shown to alter the bioavailability of BCS Class III drugs APC. The present research work was aimed to develop APC-gastro resistant tablets by gastro resistant method to match the dissolution profile with reference product. The following variables were studied in the research manufacturing process, qualitative and quantitative composition. Various formulations have been studied for APC-gastro resistant tablets' the reproducibility trial was been taken and confirms that the composition and manufacturing process found to be robust in terms of manufacturing the APC-gastro resistant tablets.

Key Words: Acamprosate tablets, GABA, gastro resistant, gastro resistant.

Introduction

Alcoholism is one of the most prevalent substance dependence disorders in the world. Acamprosate tablets have been in clinical use for more than few decades for the indication of maintaining abstinence in alcohol-dependent patients in USA and many European countries. (1) Acamprosate, N-Acetyl homotaurine, is a synthetic compound with a chemical structure similar to the amino acid neurotransmitter gamma-amino butyric acid (GABA) and the amino acid neuromodulator taurine. Recommended dosage regimen is two 333-mg tablets taken orally three times a day.(2) Acamprosate is absorbed *via* the gastrointestinal tract, with pharmacokinetic linearity in terms of dose and time. The mean maximum plasma concentration (C_{max}) of acamprosate was 180 ng/ml; following oral administration of a single 2 × 333 mg dose. The bioavailability 11%; protein binding negligible, acamprosate is not metabolized by the liver, the pharmacokinetics of APC are not altered in patients with mild to moderate hepatic insufficiency. Elimination half-life is 20 h to 33 h and excretion through the kidney.(3&4), APC considered being BCS Class III drugs, having a good solubility but poor permeability, which leads to an overall poor bioavailability. Furthermore, poor stability and short plasma half-life are major drawbacks.(5) In current research the through active excipients, the absorption of low permeability drugs can be affected to a greater extent by the use of excipients. Hence, the aim of the study is to develop APC Gastro resistant tablet

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formulation and evaluation comparison with the market product. And the objectives are to pre-formulation and formulation, evaluation to get prototype formulation.

Materials and methods

APC (Jigs Chemical Limited), Crospovidone XL 10 (Ashland specially ingredients), Microcrystalline cellulose (MCC) PH 101(Signet chemical corporation), Magnesium silicate (Tarus chemicals P LTD), Sodium Starch Glycolate (DFE Pharma), Povidone K29/32 (Lepid life sciences private limited),Colloidal silicon dioxide (Cabotsanmar limited), Magnesium Stearate (Sudeep pharma), Eudragit L 30 (Wholesale Trader of Chemical Liquid), Talc (Zilon Sawa Minerals pvt.Ltd) and Propylene glycol (Vizag chemical industry).

Instruments and Methods

Electronic balance (Sartorius), Disintegration test (Electro lab), Hardness test (Electro lab), Moisture Analyser (Sartorius), Electromagnetic sieve shaker (Electro lab), Automated tab density shaker (Electro lab),Compression machine (Karnavati), Tablet Friabilator (Electro lab) , Rapid mixer Granulator (Anchor mark), Rapid dryer (Retsh), Vibratory shifter (Anchor mark), Automated tab density tester (Anchor mark), Dissolution apparatus (Electro lab), High performance liquid chromatography (Agilent).

Formulation and development

There are several trials were done for the optimizing APC Gastro resistant tablet; in trial 1 direct compression approach was adopted. The following ingredients APC, Crospovidone XL 10, Microcrystalline cellulose, magnesium silicate, sodium starch glycolate, Colloidal silicon dioxide, magnesium stearate were mixed and subjected for direct compression approach. By the direct compression process improper flow was observed which is not feasible. In next wet granulation approach at the time of compression flow has been improved but capping tendency was been observed and density and compressibility index was been observed less. Based on the above observation it has been concluded that the wet granulation approach feasible for developing the APC-gastro resistant tablets. In next trail, the formulation itself was altered by adding the APC, Crospovidone XL 10,Microcrystalline cellulose , Magnesium silicate, Sodium Starch Glycolate, Povidone K29/32,Colloidal silicon dioxide, Magnesium Stearate, Eudragit L 30,Talc and Propylene glycol were added. During the time of compression, flow has been improved and capping tendency has been decreased, but the disintegration time was more. Further to decrease the DT time, povidone has to be reduced in the next trial.

In final trail wet granulation approaches, to improve the dissolution profile in the tablets, by reducing the povidone content and introduction of microcrystalline cellulose in extra granular part was performed. The physical parameters of the tablets were found to be satisfactory and final formula was shown in **Table 1**.

In *vitro* evaluation and Characterization of APC blend

The flow properties of APC blend was characterized by measuring angle of repose, bulk density and tapped density, Carr's compressibility index and Hausner's ratio and the results are tabulated in **Table 2**.

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Angle of repose (6)

The frictional forces of the liquisolid APC blend was measured for its angle of repose (θ) using funnel method. 20 gm of the liquisolid APC blend was taken in a funnel, the height of the funnel was adjusted and the tip just touched the apex of the heap of the granules blend (a distance of 10 cm from the flat surface). The APC blend was allowed to flow through the 10 mm funnel orifice by removing the cotton plug from the funnel orifice, the height of the heap (h) formed as well as the radius of the heap (r) and the diameter of the APC blend heap was noted. Further, the angle of repose was calculated using the following equation:

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

θ = Angle of repose, h = height and r = radius of APC blend heap.

Loose bulk density and tapped bulk density (7)

The loose bulk density (LBD) and tapped bulk density (TBD) was evaluated for the APC liquid solid blend by standard procedure, 20 gm of APC blend was weighed on a chemical balance and transferred into a 100 ml measuring cylinder. The cylinder was dropped on a wooden platform from a height of 2.5 cm three times at 2 sec intervals. The volume occupied by the APC blend was recorded as the bulk volume. The cylinder was then tapped on the wooden platform up to the volume occupied by the blend remains constant. The tapping was then extended until no further change in volume was noted. LBD and TBD were calculated using the following:

$$\text{LBD} = \frac{\text{Weight of the blend}}{\text{volume of the packing}}$$

$$\text{TBD} = \frac{\text{Weight of the blend}}{\text{tapped volume of the packing}}$$

The data obtained was used for calculating the Carr's compressibility index and Hausner's ratio as below.

Carr's compressibility index (8)

Carr's compressibility index determinations are an indirect measure of bulk density, cohesiveness, moisture content, size / shape and surface area of APC blend can influence the observed compressibility index. The APC blend was evaluated for the influences the flow properties of Compressibility Index (Carr's Index) was determined by using the following,

$$\text{Carr's compressibility Index (\%)} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio (8)

Hausner's ratio is an indirect index of measure of ease of powder flow characters and was calculated by the following,

$$\text{Hausner's Ratio} = \text{TD} / \text{BD}$$

TD=Tapped Density, BD = Tapped density.

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Evaluation of APCs tablets:

The prepared APC tablets were designed to contain a specific amount of APC as specified in manufacturing formula. Different quality control parameters for APC were investigated by adopting the method described in Indian Pharmacopeia 2010.

Weight variation test (9)

The weight variations of APC ten tablets of the prepared formulation were done using an electronic balance and the test was performed according to the official method and their average weight was calculated.

Thickness (10)

Ten tablets from each formulation were taken randomly and their thickness was measured with a digital screw gauge micrometer (Mitutoyo, Japan). The mean SD values were calculated.

Hardness (11)

Hardness or crushing strength of the tested orally disintegrating tablet formulations was measured using the tablet hardness tester (Monsanto type).

Friability test (12)

The friabilator was used to test the friability of APC tablets, which is a measure of their strength. The APC tablets are subjected to abrasions and shock in a plastic chamber that rotates at 25 rpm and drops the tablets from a height of 6 inches with each revolution. Twenty APC tablets were pre-weighed and subjected to 100 revolutions in the friabilator. APC tablets were dedusted and reweighed using a soft muslin cloth. The following formula was used to calculate percent friability (percent F):

$$\% F = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weightFriability}} \times 100$$

Drug content (13)

The mobile phase was prepared by mixing methanol and buffer in the ratio of 30:70 v/v and later it was sonicated for 10 minutes for the removal of air bubbles. Reverse phase C18 column, Phenomenex Luna (250 X4.6 mm; 5µ), mobile phase consisting of a mixture of methanol:triethylammonium phosphate buffer (adjusted to pH 3.0 with 30% v/v of ortho phosphoricacid) in the ratio of 30:70, v/v. The mobile phase was set at a flow rate of 0.5 ml/min and the volume injected was 20 µl for every injection. Ten tablets were weighed separately and the average weight was determined. The average weight was weighed from the ten tablets grinded in a pestle and mortar, transferred to a 100 ml volumetric flask containing 100 ml diluent and then stirred for 20 minutes, followed by filtration through 0.45µ nylon membrane filter to get sample stock solution of 3.33mg/ml. 1 ml of the above stock solution was pipetted out and made up to 100 ml to get working sample solution equivalent to a

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concentration of working standard of 33.3 µg/ml. The detection wavelength was set at 215 nm.

Disintegration time (14)

The *in-vitro* disintegration time was determined using disintegration test apparatus. Six APC tablets were placed in each of the six tubes of the disintegration test apparatus. The basket with the bottom surface made of a stainless-steel screen (mesh no.10) was immersed in water bath at 37 ± 2°C the time in min taken for complete disintegration of the APC tablets with no palpable mass remaining in the apparatus was measured in min.

Dissolution test (15)

The dissolution test was conducted according to USP pharmacopeia. A buffer was prepared from potassium phosphate (pH 5.8) with a temperature maintained at 37±1°C throughout the experiment. The samples were withdrawn after 30, 60, 90,120 and 180 min and the equivalent amount of fresh buffer solution was immediately introduced as a replacement. The samples were filtered and assayed for drug content by measuring the absorbance at at 215 nm using a UV spectrophotometer. Phosphate buffer was used as a blank the same was repeated for marketed reference tablet also.

Table 1 F 4:- Wet granulation approach

S.No	Name of the ingredients	mg/unit
1	APC	333.00
2	Crospovidone XL 10	10.00
3	Microcrystalline cellulose (MCC) PH 101	90.00
4	Povidone	10.00
5	Sodium Starch Glycollate	10.00
6	Colloidal silicon dioxide	3.00
7	Microcrystalline cellulose PH 102	35.00
8	Magnesium silicate	30.00
9	Magnesium stearate	7.00
Total weight of the core tablet (mg)		528.00
10	Eudragit L 30	38.00
11	Talc	6.00
12	Propylene glycol	4.00
Total weight of the tablet (mg)		573.00

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Table 2 Pre-Compression Parameters-Data for pre-Compression Parameters of tablet Formulation (F1-F4)

Formulation	F1	F2	F3	F4
Bulk Density (g/ml)	0.47	0.41	0.60	0.61
Tapped Density (g/ml)	0.89	0.81	0.74	0.72
Compressibility Index (%)	47.19	49.38	18.91	15.28
Hausner Ratio (HR)	1.89	1.98	1.23	1.18

Table 3 Data for Post-Compression Parameters of tablet Formulation (F4)

Formulation (F4)	Average N=6
Weight Variation (mg)	528.2
Thickness (mm)	6.24
Hardness (kg/ cm 2)	70.19
Friability (%)	0.02
Drug Content (%)	98.7
Disintegrating Time (min)	42.49 min

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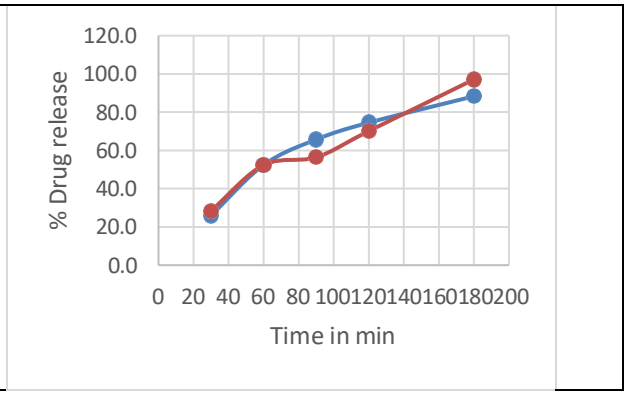
Table 4 *Invitro* dissolution release rate studies of APC – GRT

Time (Min)	Reference product	F4
30	26.0	28.4
60	52.4	52.4
90	65.7	56.4
120	74.5	75.1
180	88.3	97.1



From the above results it was concluded that the bulk density, tapped density, compressibility index, Hausner ratio of pre-Compression parameters for the tablet formulation were satisfactory and the prepared blend had good flow properties based on these results. The post-compression parameters of tablet formulation like weight variation, thickness, hardness, friability, drug Content and disintegrating time was within the range as per expected results. The *Invitro* dissolution release rate studies of APC – GRT confirms robust in terms of manufacturing the APC-gastro resistant tablets with innovator products. From the above data can be concluded the formulation code F4 shows similar invitro dissolution profile compared to reference product.

Conclusion

The present research work APC-gastro resistant tablets were developed by wet granulation method to match the dissolution profile with reference product and the following

variable were studied *viz* formulation process, qualitative composition and quantitative composition. Reproducibility trial was been taken and confirms that the composition and manufacturing process found to be robust in terms of manufacturing the APC-gastro resistant tablets.

Conflicts of interest: None declared.

Ethical approval: Nil

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