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Formulation and Evaluation of Acamprosate Calcium Implant using Poly (Lactic-co-glycolic acid)

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Abstract

This present research study was carried out to develop and evaluate the implants of Acamprosate calcium by using biodegradable polymeric material PLGA. Acamprosate calcium is commonly used in treatment of alcoholism as abuse deterrent. Implants were prepared by using PLGA as polymer and magnesium stearate as a plasticizer under controlled environment. The implants, weighing approximately 180 mg were evaluated for thickness, hardness, friability, weight variation, drug content uniformity and drug polymer interaction. In vitro drug release studies were conducted in phosphate buffer pH 7.4

Key-Words: Acamprosate calcium, PLGA, Magnesium stearate, implants, Alcoholism, Abuse deterrent

Introduction

Alcoholism, also known as alcohol dependence, is a disabling addictive disorder, characterized by compulsive and uncontrolled consumption of alcohol despite its negative effects on the drinker's health, relationships, and social standing. Like other drug addictions, alcoholism is medically defined as a treatable disease. Various drugs like Disulfiram, Nalmefene, Naltrexone, Ondansetron, Calcium carbimide, and Topiramate are available in tablet and implant dosage forms for the treatment of alcoholism. Acamprosate calcium is also useful in treatment of alcoholism. Acamprosate calcium has antagonising effect on the actions of glutamate, a neurotransmitter which is hyperactive in the post-withdrawal phase. [1-3] It is available in tablet formulation under brand name of Campral. Campral is immediate release formulation having short duration of action. No sustained release formulation of Acamprosate calcium is available in market. References to development of sustained release formulation of Acamprosate calcium are not available in literature. Hence, there exists need to develop sustained release formulation of Acamprosate calcium having longer duration of action. Present study aims to develop and evaluate sustained release subcutaneous implant formulation of Acamprosate calcium useful in treatment of alcoholism.

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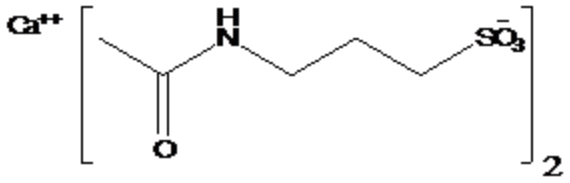

Figure1: Acamprosate calcium [4]

Material and Methods

Drug & Chemicals:

Acamprosate calcium was procured from Emcure Pharmaceuticals, Pune,Potassium dihydrogen phosphate, PLGA, magnesium stearate,sulphuric acid,sodium tripoly phosphate,trisodium citrate,sodium alginate,PVP K30,chitosan and all the other reagents used were of analytical grade.

Methods:

Excipient selection and characterization: The composition of Acamprosate calcium implant formulation was selected based on the available implant formulations. Table.1 lists the composition of Acamprosate calcium implant formulation. The same types of excipients as the available implant formulations were chosen. Excipients levels were based on inactive ingredient database (IID) limits and experience with FDA-approved dosage forms.[5] Table.2 lists the IIG limits represent the maximum

level of use of an excipients in a dosage form that has been approved by the U.S.FDA in a certain route of administration. Acamprosate calcium used was of pharmacopoeia grade. Acamprosate calcium was evaluated as per USP standards. All the excipients used were of pharmacopoeia grade. Excipients were evaluated as per USP standards.

Color, odor and appearance:

The drugs and excipients were evaluated for their color, odor and appearance and melting point as per the standard methods Table 3.

Drug and excipient characterization:

The acamprosate calcium and excipients characterized by IR spectroscopy as per standard method available in literature of which spectra is shown in figure 1 and 2 and specific peaks in table 4 and 5 respectively.

Preparation of acamprosate calcium implant formulation:

Direct compression method was used in preparation of Acamprosate calcium implant formulation. Acamprosate Calcium, Poly lactic co-glycolic acid (PLGA) and Magnesium stearate were weighed accurately and passed through 60# sieve. The physical dispersion of the Acamprosate Calcium, PLGA and Magnesium stearate was prepared by direct mixing. The compression of powder blend was done on rotary compression machine (Jaguar) using 8 mm flat-faced circular punches at a constant force to achieve the hardness of 4-5 kg/cm^2. Prepared implants were stored at room temperature in an airtight amber colored glass vials with cotton packing for further study.

Evaluation:

Thickness, diameter, hardness and weight variation of implant formulations:

The thickness, diameter and hardness of implants was determined using a Micrometer Screw Gauge (Japan), Pfizer hardness tester (Cadmach, Ahemedabad, India) respectively. Five implants from each batch of formulation were used and the mean thickness, diameter,hardness and weight variation with respective standard deviation (SD) were determined.

Friability of implant formulations:

The friability test was carried out in an instrument called a friabilator (Roche friabilator). This instrument consisted of a plastic chamber for placing the implants which is attached to a horizontal axis. The drum has an inside diameter of 287mm and is about 38mm in depth, made of a transparent synthetic polymer with polished internal surface. A set of pre weighed implants [n=10] were placed in the plastic chamber revolving at 24-25 rpm for 4 min. The implants were subjected to combined effects of abrasion and shock. The implants were dropped at a distance of six inches on each revolution. The instrument was operated for 100 revolutions after which the implants were dusted and reweighed.

The percent friability of implant was then calculated using formula

$$\text{Friability } (\%) = \frac{\text{Wt} - \text{Wo}}{\text{Wo}} \text{ X } 100$$

Where, Wo initial weight of implants,

Wt weight of implants after 100 revolutions

The results of the above parameters shown in table 6.

Drug content:

Acamprosate Calcium content of implants was estimated by removing a sample of one implant from every batch. The implant sample was placed in a beaker containing 100 ml of 50:50 mixture of methanol and water and kept under magnetic stirring (50 rpm) at room temperature for 24 hr. After 24 hr the dispersion was filtered using Whatman filter paper grade 41 to remove insoluble excipients. The filtrate was diluted appropriately and the drug content was determined using Shimadzu UV 2501 PC, double beam, spectrophotometer at 1.0 nm slit width using Phosphate buffer pH 7.4 as a blank at 207 nm. The selected batch of formulations drug content was found to be 98.77%. Such value is within the limits.[6-8]

Swelling study:

The swelling behavior of the implant was measured and identified by taking the images of implants using Olympus microscope with inbuilt camera before and after the study. A known weight of implant was immersed in 30 ml phosphate buffer pH 7.4 for the required period of time. The swollen weight of the implant was determined by first blotting the implant with filter paper. The weight of swollen implant was recorded at various time period of 0.5,2,4,8,12, 16, 20, 24 hrs.[9]

The percent swelling of implant was then calculated using formula

$$\text{Swelling Index (S)} = \frac{\text{Wt} - \text{Wo}}{\text{Wo}} \text{ X } 100$$

Where, S is swelling index of implant,

Wo initial weight of implant,

Wt weight of implant after time t

Of which results are shown in figure 3 and table 7.

In vitro drug release study:

Drug release from the prepared implant formulations was studied by Vial method. Implants were placed into 30.0 ml screw capped glass vials with diameter-25 mm containing 25 ml phosphate buffer pH 7.4. Vials were kept at room temperature for 30 days without agitation and were only shaken for 5.0 minutes before sampling time. At defined time points, 5ml of the dissolution

medium was replaced with fresh buffer. Each 5.0 ml of sample solution was filtered through Whatman filter paper grade 41. Appropriate dilution was prepared using phosphate buffer pH 7.4 and absorbance of resulting solutions were measured at 207 nm. Drug concentration in the sample was determined using standard calibration curve.[10] Cumulative percent drug release was determined at each point. Figure 4 and table 8.

Results and Discussion

The different excipient mentioned in table 1 does not show results as per the requirement of implantable sustained delivery. The melting point of drug and selected excipients in the formulation shows the results as per the requirement, the hardness, thickness, weight variation, friability and content uniformity are found within the acceptable limits of implant formulation.

Drug polymer interaction studies by FTIR spectroscopy revealed that there was no physical interaction recorded suggesting that the Acamprosate Calcium is compatible with PLGA and magnesium stearate which were used for implant formulations. There were no major changes in peak positions (1182, 1380, 1425, 1696 and 3394 cm^{-1}) seen in the FTIR spectra of Acamprosate Calcium (Figure1) and in a physical mixture of Acamprosate Calcium with PLGA and magnesium stearate (Figure 2).

The swelling study of formulation higher value and photographs (Figure 4) indicates that the formulation is well suited for long term sustained delivery of polymeric matrix containing drug. It is confirmed from in vitro dissolution studies that formulation is well suited for the sustained delivery up to 28 days.

Conclusion

Sustained release implantable tablets of Acamprosate calcium were prepared successfully using PLGA polymer and magnesium stearate as a plasticizer which retards the release and achieve required dissolution profile. Release profile was governed by determining swelling index and in vitro dissolution and hardness as well as thickness of implant formulation could be modified by changing the amount and type of polymer in polymeric implant tablet formulation.

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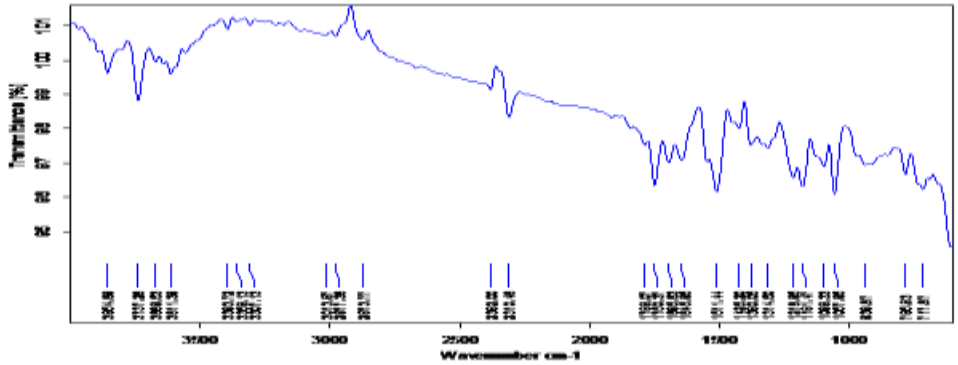

Figure 1: IR spectra of Acamprosate calcium

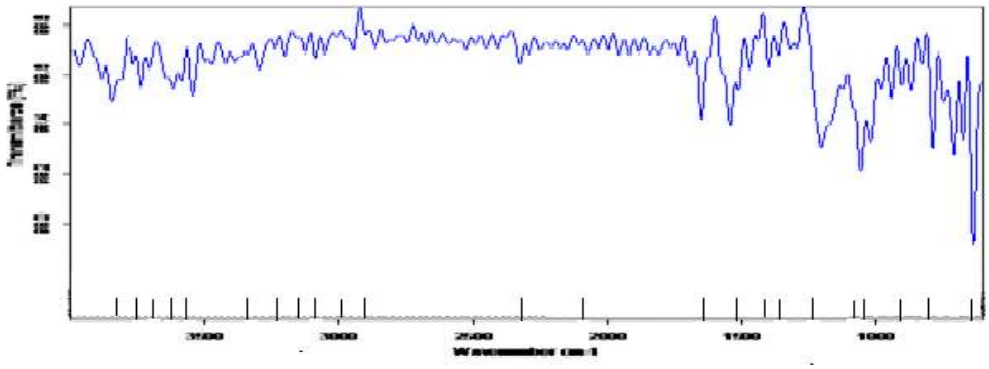

Figure 2: IR spectra of Acamprosate calcium with excipients

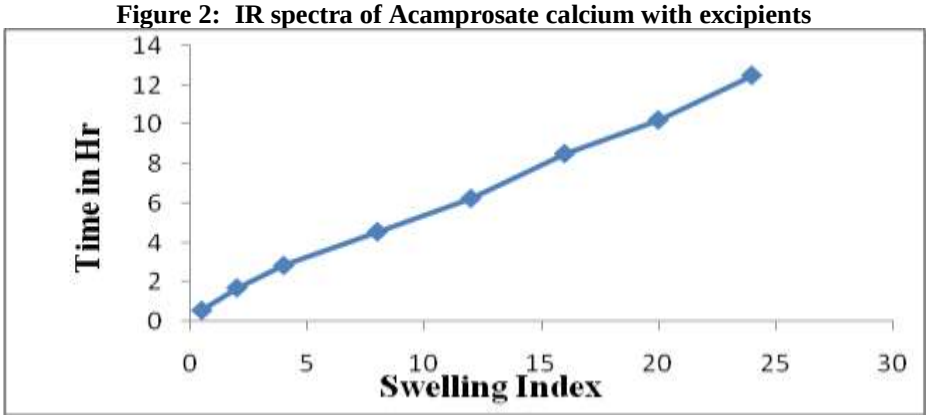

Figure 3: Swelling index graph of selected batch of formulation

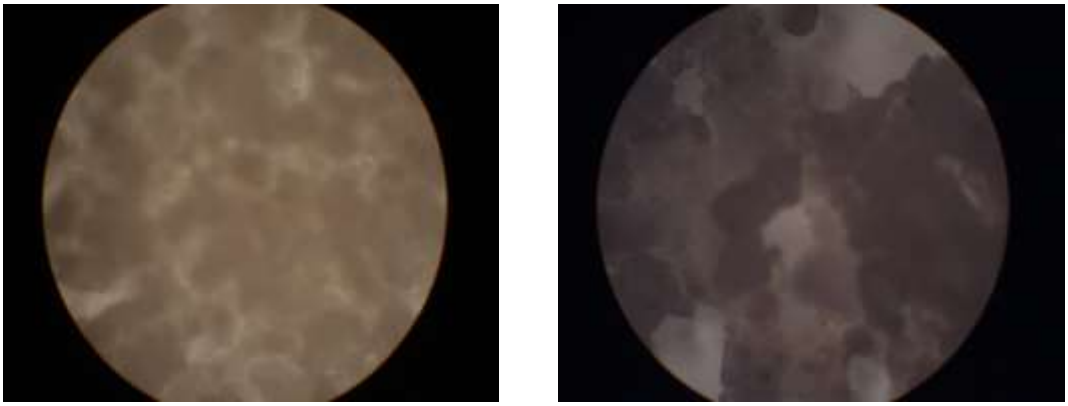

Figure 4: Swelling index photographs of selected batch before and after swelling respectively

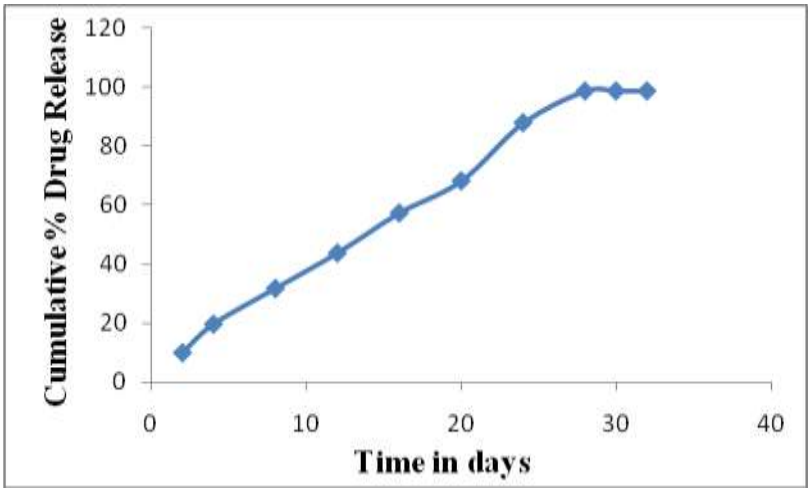

Figure 4: Cumulative % drug release graph of selected batch of formulation

Table 1: Composition preliminary batches of Acamprosate calcium implant formulation

Parameters	P1	P2	P3	P4	**P5***
Chitosan	35	35	35	35	--
C-TPP	40	--	--	--	--
C-TSC	--	40	--	--	--
C-H2SO4	--	--	40	--	--
C-Na alginate	--	--	--	40	--
HPMC K4	10	10	10	10	--
PVP K30	5	5	5	5	--
PLGA	--	--	--	--	**88**
Mg.stearate	--	--	--	--	**02**
Acamprosate ca	90	90	90	90	**90**
Total wt.(mg)	180	180	180	180	**180**

Table 2: Composition & IIG limits inactive ingredients of implant formulation

Component	Function	Specifications	Amt. used in formulation(mg)	US-FDA IIG Limit
Acamprosate calcium	Drug substance	USP	90	----
PLGA	Biodegradable polymer	USP-NF	88	116
Magnesium stearate	Plasticizer	USP-NF	02	3.4

Table 3: Physical characterization of drug and inactive ingredients of implant formulation

Sr.no.	Parameter	Acamprosate calcium	PLGA	Magnesium stearate
1	Color	White or colorless	White or colorless	White or colorless
2	Odor	Odorless	Odorless	Odorless
3	Appearance	Crystalline powder	Crystalline powder	Fine smooth powder
4	Melting Point	268-271^0 C	389-391^0 C	270-273^0 C

Table 4: IR spectra characterization of Acamprosate

Functional Group	Wavelength cm^{-1}	Significance
C=O	1695.63	Streching
N-H	3393.72	Streching
S=O	1380.05 1181.47	Streching(Symmetric) Bending(Assymetric)
C-H	1425.20	Streching

calcium

Table 5: IR spectra characterization of Acamprosate calcium with excipients

Functional Group	Wavelength cm^{-1}	Significance
C=O	1694.01	Streching
N-H	3372.90	Streching
S=O	1364.01 1123.45	Streching(Symmetric) Bending(Assymetric)
C-H	1471.58	Streching

Table 6: Evaluation of Acamprosate calcium implant of selected batch

Formulation Parameter	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Weight variation	Friability (%)
Acamprosate calcium (90mg) PLGA(88mg) Mg.stearate(2mg)	2.89± 0.035	8.03 ±0.14	4.52 ±0.192	180±0.29	0.005

Table 7: Evaluation of swelling index of selected batch

Time in Hours	Swelling Index
0.5	0.56
2	1.7
4	2.84
8	4.55
12	6.25
16	8.52
20	10.23
24	12.5

Table 8: Cumulative % drug release of selected batch

Time in days	Cumulative % Drug release
2	9.83
4	19.52
8	31.67
12	43.72
16	57.33
20	68.23
24	87.98
28	98.74
30	98.77
32	98.77

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