PREPARATION OF ORAL CONTROLLED RELEASE TABLETS OF LACOSAMIDE AND INVITRO EVALUATION

Janat beula
Associate professor
Pharmaceuticus
TRR College of pharmacy
Meerpet Hyderabad

K. CHAITANYA PRASAD
ASSISTANT PROFESSOR
DEPARTMENT OF
PHARMACEUTICAL CHEMISTRY
SAMSKRUTHI COLLEGE OF
PHARMACY ,Hyderabad

ABSTRACT

The oral controlled release system of many drugs has been known to be an essential part of formulation development in drug delivery systems. It has been the focus of pharmaceutical research for many years due to its various advantages over conventional dosage forms. Administering the drug for release in the blood at a controlled rate, to maintain relatively constant drug levels in plasma over a controlled period of time, can overcome many problems associated with conventional dosage forms. The applicability of these dosage forms is due to reduction in the frequencies of drug dosing, which lead to patient convenience and compliance. In addition, a reduction of wide fluctuations in plasma drug concentration peak can be obtained. As a result, toxicity and poor efficacy can be avoided, especially with drugs of narrow therapeutic indices. Such problems, associated with conventional dosage forms of many drugs, can be overcome by using controlled release drug delivery systems, to deliver the drug for absorption at a controlled rate over an extended period of time. The controlled release dosage form should be tailored so that variations in the components can lead to predictable alterations in the drug release profiles. Various controlled release drug delivery systems have different mechanisms to control the drug release rate, such as the osmotic pump, ion exchange resin and matrix systems which have been widely utilized as controlled release drug delivery approaches. Besides, polymers have often been used in the components of controlled release drug delivery systems. A sustained release profile, without occurring of the dose dumping, and sufficient bioavailability can be achieved when a drug is embedded in some polymeric materials such as gelucires. The presant work focuses on preparing lacosamide controlled release(CR) tablets

KEYWORDS : Lacosamide, CR etc,.,

INTRODUCTON

Oral drug administration is the most preferable and oldest route for drug delivery. This is due to the low cost of medicine preparation and ease of administration, which makes it the most favorable route of drug administration for patients. It has been known as the most popular and successful route for controlled delivery of fast release drugs because of greater flexibility in the designing of dosage forms compared to other routes. Previous reviews reported that more than 50% of the medications which are available in the market were found to be given orally.

Research on oral drug delivery with either further development in the delivery system or novelty in the drug formulation is ongoing work for many formulation scientists. The most prominent requirements for a drug delivery system to make it novel are, first to deliver a drug at a controlled rate, and second to pass the active entity to the target site for action. Formulation scientists have been used many possible approaches to achieve this challenging novelty in oral drug formulation, either by unifying drug distribution into a carrier system, or by controlling drug release in the blood to reach the designed plasma drug concentration-time profile.

Various systems of oral controlled release dosage forms

Various techniques have been used in the preparation of the controlled release drug delivery system; most of them working under the principle of slowing the dissolution rate of the drug from the dosage form. In general, controlled release formulations can be divided into different categories based on methods of preparation and/or the mechanisms of drug release, which will be shown in the following below.

Hydrophilic matrix system

This is also known as the swellable controlled release drug delivery system. In this type of matrix system the drug substances are mixed with a hydrophilic gelling agent. Three different groups of polymers are used in the preparation of hydrophilic matrices. These groups are as follows: 1) Cellulose derivatives such as hydroxyethyl cellulose, hydroxypropylmethyl cellulose (HPMC) 25, 100, 4000 and 15000 cps, sodium carboxymethyl cellulose (CMC) and methyl cellulose 400 and 4000 cps. 2) Non-cellulose natural or semi synthetic polymers [17] such as agar-agar, carob gum, alginates, molasses, polysaccharides of mannose and galactose, chitosan and modified starches. 3) Polymers of acrylic acid such as carbopol 934. On the other hand, other hydrophilic materials can also be used such as alginic acid, gelatin and natural gums.

Clinical Trials Data on Adverse Events and Long-Term Safety

Based on the three pivotal clinical trials previously discussed, LCM appears to be well tolerated. Most adverse events were mild to moderate and were more commonly observed during the titration phase. The most common adverse events were related to CNS and gastrointestinal side effects, and they appeared to be dose related. The two studies comparing 400 mg/day and 600-mg/day dosing revealed that the emergent adverse events leading to discontinuation of LCM were dizziness, nausea, diplopia, abnormal coordination, ataxia, vomiting, and nystagmus. Of these, dizziness was the most common. LCM appears to have a low incidence of psychiatric side effects with psychosis reported in only 0.3% of patients (18). There is no report of rash, hyponatremia, or cognitive slowing. There is no evidence of abuse potential. Among other clinically relevant side effects seen with other AEDs, LCM does not cause weight gain or weight loss, neither does it change patterns in hematology, blood chemistry, and vital signs (15,17,19). The percentage of patients who withdrew from the studies increased with higher doses, particularly with the 600-mg/day dose (see Figure 3). Although the LCM efficacy data may be slightly better for 600 mg/day than 400 mg/day, when data from all three clinical trials are pooled, the tolerability of LCM is better at 400 mg/day, thus making it appear to be the optimal dose.

AIM AND OBJECTIVE

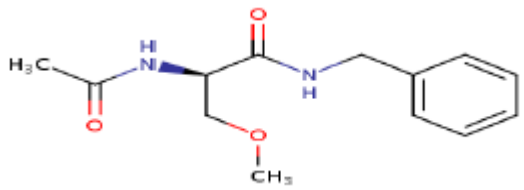
In the present study it has been aimed at developing tablets of Lacosamide with a view of minimizing the drug release in the physiological environment of stomach and small intestine and then release in small intestine. The main objective of This study was conducted to develop controlled drug delivery of Lacosamide.

DRUG PROFILE

Drug name : LACOSAMIDE

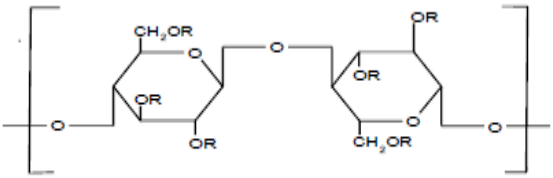
Category : Anticonvulsants

Iupac name : (2R)-N-benzyl-2-acetamido-3-methoxypropanamide
Synonyms : Harkoseride, Erlosamide, SPM 927, Vimpat.
Description : Lacosamide is a white to light yellow powder.Lacosamide is a functionalized amino acid that has activity in the maximal electroshock seizure test, and is indicated for the adjunctive treatment of partial-onset seizures and diabetic neuropathic pain.
Recent studies indicate that Lacosamide only affects those neurons which are depolarized or active for long periods of time, typical of neurons at the focus of an epileptic seizure, as opposed to other antiepileptic drugs such as carbamazepine or lamotrigine which slow the recovery from inactivation and reduce the ability of neurons to fire action potentials.
Melting point : 140-146˚C
CAS NO : 175481-36-4
Structure:-



Molecular formula : C13H18N2O3
Molecular weight :
Average: 250.2936 Monoisotopic: 250.131742452 g/mol.
Bioavailability : high
Half-life : 13 Hours
Protein binding : <15%
Dosage forms : injection,tablet(film coated)
Dose : 50,100,150,200mg. 10mg/ml.
Pharmacodynamics :
Lacosamide therapy is correlated with a decrease in seizure frequency. It should be noted that in group analyses, dosages above 400 mg/day do not appear to result in additional benefit.
Mechanism of Action:
It is proposed that lacosamide's inhibition of sodium channels is responsible for analgesia.
Lacosamide may be selective for inhibiting depolarized neurons rather than neurons with normal resting potentials. Pain and nociceptor hyperexcitability are associated with neural membrane depolarization. Lacosamide binds to collapsin response mediator protein-2 (CRMP-2), a phosphoprotein which is expressed primarily in the nervous system and is involved in neuronal differentiation and control of axonal outgrowth. The role CRMP-2 of binding in seizure control is hasn't been elucidated.

EXCIPIENTS PROFILE
Hydroxy Propyl Methyl Cellulose (HPMC)2,,17,45
Nonproprietary names-
BP : Hypromellose
PhEur : Methylhydroxypropylcellulose
USP : Hydroxy propyl methyl cellulose
Synonyms : HPMC, Methocel, Methyl cellulose propylene glycol ether,Methyl hydroxyl propyl Cellulose ,Metolose, Pharmacoat,Cellulose, Hydroxy propyl methyl ether ,Culminal MHPC; E464.
Iupac name : (2r,3r,4s,5r,6r)-2,3,4-trimethoxy-6-(methoxymethyl)-5-((2s,3r,4s,5r,6r)-3,4,5-trimethoxy-6-(methoxymethyl)oxan2yl)oxyoxane;1-(((2r,3r,4s,5r,6s)-3,4,5-tris(2-hydroxypropoxy)-6-((2r,3r,4s,5r,6r)-4,5,6-tris(2-hydroxypropoxy)-2-(2-hydroxypropoxymethyl)oxan-3-yl)oxyoxan-2-yl)methoxypropoxymethyl)oxan-3-yl)methoxy)propan-2-ol.
Molecular formula : C12H23O6 (C12H22O5)n C12H23O5 where and can vary to provide a wide variety of molecular weights.
Structural formula



Where R is H, CH_3 or CH_3-CH(OH)-CH_2

Molecular weight : 10,000 - 15, 00,000

Description : Hydroxy propyl methyl cellulose is a tasteless, and white to slightly
off white to slightly off white, fibrous or granular powder.

Melting Point : Browns at 190-2000C, chars at 225-2300C

Stability and storage : It is stable although it is slightly hygroscopic. The bulk material should
be stored in an airtight container in a cool and dry place. Increased in temperature reduces the
viscosity of the solution.

METHODOLOGY

PREPARATIONOFGRAPH OF LACOSAMIDE (in 0.1NHCl, 6.8 PH, 7.4 pH BUFFERS)

Accurately weighed amount of 100 mg of Lacosamide was transferred into a 100 mL volumetric flask. This gives a solution having concentration of 1mg/mL, of Lacosamide stock
solution. From this primary stock 10mL was transfer red into another volumetric flask and
made up to 100mL with simulated gastricfluid(0.1NHCl,pH1.2),from this secondary stock0.1,
0.2,0.3, 0.4,0.5, 0.6and 0.7 mL, was taken separately and made up to 10 ml with 0.1N HCl (pH
1.2) solution, to produce 1,2, 3,4, 5, 6 and 7 µg/ mL respectively. The absorbance was measured
at 250 nm using a UV-Visible spectrophotometer. Calibration curve values were shown in the
following Table. The calibration curve of Lacosamidein SGF was (pH 1.2) shown in Figure. In the similar way curves of Lacosamidein SIF (pH 7.4and pH 6.8) were shown at 250nm.

DRUG – EXCIPIENT COMPATIBILITY STUDIES:

Fourier Transform Infra Red (FTIR) spectroscopy:

The physical properties of the physical mixture were compared with those of plain drug.
Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted
under vacuum at a pressure of about 12 psi for 3 minutes.The resultant disc was mounted in a
suitable holder in Perkin Elmer IRspectrophotometer and the IR spectrum was recorded from
3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Differential Scanning Calorimetry (DSC):

DSC scan of samples were obtained in a Perkin Elmer thermal analyzer equipped with
a monitor and printer. The instrument was calibrated with indium. Accurately weighed 5mg of
sample were placed in an open, flat bottom, aluminium sample pans. Ther mograms were
obtained by heating the sample at a constantrate10minute. A dry purge of nitrogen gas
(20ml/min) was used for all runs sample heated from 35oC to 400oC.

PREPARATION OF BLEND FOR LACOSAMIDE :

The composition of the blend includes (Table 5) Lacosamide, HPMC K4M, HPMC
K15M, HPMC E15LV which were passed through sieve80 individually and were mixed with already sieved Talc, Magnesium stearate, MCC in mortar and pestle and were subjected to
different pre formulation parameters.

PREFORMULATION PARAMETERS:

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose . It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual ntil the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical.

$\tan\theta = h / r$

Where; $\tan\theta$= Angle of repose; h = Height of the cone; r = Radius of the cone base

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Table 6: Angle of Repose values (as per USP)

Bulk density:

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10gm powder blend was sieved and introduced into a dry 20mlcylinder, without compacting. The powder was carefully levelled without compacting and the unsettled apparent volume, Vo, was read

The bulk density was calculated using the formula:

Bulk Density = M / Vo

Where,

M = weight of sample

Vo = apparent volume of powder

Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (I ndividual weight – Average weight / Average weight) × 100

Average weight of tablet (mg) (I.P)	Average weight of tablet (mg) (U.S.P)	Maximum percentage difference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	5

Drug release studies of Lacosamide tablets:

The release of Lacosamide from tablets was carriedout using USP paddle-type dissolution apparatus at a rotation speed of50 rpm, and a temperature of37±0.5 °C. For tablets, simulation of gastrointestinal

transit conditions was achieved by using different dissolution media. Thus, drug release studies were conducted in simulated gastric fluid for the first 2 hours as the average gastric emptying time is a bout 2 hours.Then, the dissolution medium was replaced with enzyme- free simulated intestinal fluid and tested for drug release for 3hours, as the average small intestinal transit time is about 3 hours, and finally enzyme-free simulated intestinal fluid (SIF, pH 6.8) was used upto 12 hours to mimic colonic pH conditions. Drug release was measured from spray coated Lacosamide tablets, added to 900 ml of dissolution medium. 5 ml of sample was withdrawn every time and replaced with fresh medium, samples withdrawn at various time intervals were analyzed spectrophotometrically at 275nmand 270nm respectively. All dissolution runs were performed for six batch. The results were given with deviation.

RESULTS AND DISCUSSION

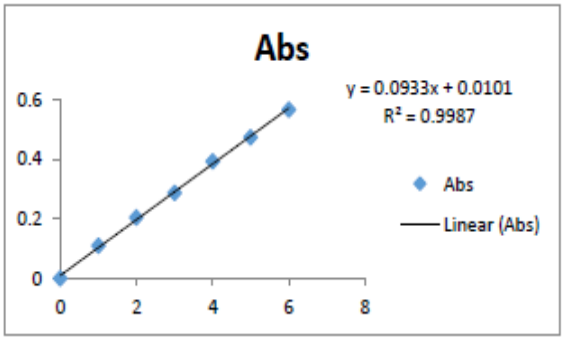
The present study was aimed to developing Lacosamide formulations for controlled release drug delivery using HPMC K4M, HPMC K15M, HPMC E15LV. All the formulations were evaluated for physicochemical properties and invitro drug release studies

ANALYTICAL METHOD

Graphs of Lacosamide was taken in Simulated Gastric fluid (pH 1.2) and Simulated
Intestinal Fluid (pH 6.8 and 7.4).

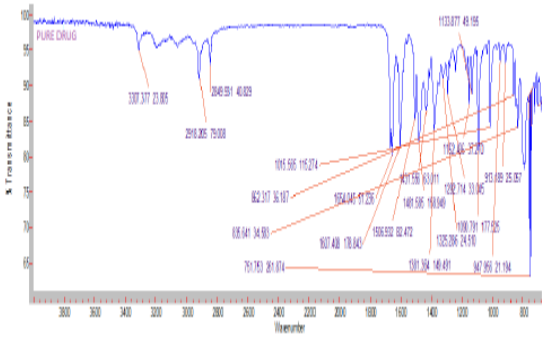
Conc [mg/l]	Abs
0	0
1	0.109
2	0.204
3	0.287
4	0.392
5	0.472
6	0.566

Observations for graph of Lacosamidein 6.8 pH



Stnaderd graph of Lacosamidein 6.8 pH

FTIR Compatability studies



PREFORMULATION PARAMETERS OF LACOSAMIDE TABLETS

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	36.01±0.62	0.55±0.27	0.645±0.13	14.72±0.62	0.85
F2	34.87±0.06	0.57±0.18	0.66±0.09	13.63±0.12	0.86
F3	32.74±0.12	0.53±0.22	0.606±0.04	14.19±0.26	0.858
F4	35.33±0.62	0.531±0.31	0.613±0.03	13.37±0.38	0.866
F5	36.24±0.05	0.549±0.14	0.641±0.17	14.35±0.54	0.856
F6	36.12±0.45	0.564±0.32	0.666±0.11	15.31±0.22	0.846

Pre-formulation parameters of blend

Lacosamide blend was subjected to various pre-formulation parameters. The apparent bulk density and tapped bulk density values ranged from0.52to0.581 and0.606 to 0.671 respectively. According to Tables 3 and 4, the results of angle of repose and compressibility index (%)ranged from 32.74±0.12 to 37.08±0.96and 13.37±0.38to 14.72±0.62 respectively. The results of angle of repose (<35)and compressibility index (<23)indicates fair to passable flow properties of the powder mixture. These results show that the core powder mixture has good flow properties. The formulation blend was directly compressed to tablets and *in-vitro* drug release studies were performed.

Dissolution Data of Lacosamide Tablets

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED	
	F5	F6
0.5	20.42	20.68
1	29.73	30.86
2	38.63	39.35
3	49.05	45.45
4	56.25	49.8
5	69.33	57.3
6	77.41	63.28
7	87.84	69.75
8	96.8	75.34
9	97.24	80.52
10		82.17
11		90.75
12		96.25

Dissolution profile of Lacosamide(F5,F6 formulations

From the dissolution data it was evident that the formulations prepared with HPMC E15LV polymer were unable to retard the drug release up to desired time period i.e., 8 hours.

Whereas the formulations prepared with HPMC K15 M retarded the drug release in the concentration of 150 mg showed required release pattern i.e., retarded the drug release up to 8 hours and showed maximum of 98.74% in 12 hours with good retardation.

The formulations prepared with HPMC K4 M showed more retardation even after 8 hours they were not shown total drug release. Hence they were not considered.

Conclusion

In the present work, an attempt has been made to develop controlled release tablets of Lacosamide. Different gradess of eudragit polymers used . All the formulations were prepared by direct compression method using 6mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F3 formulation showed maximum % drug release i.e., 98.37 % in 8 hrs hence it is considered as optimized formulation. The f3 formulation contains HPMC K15M in the concentration of 50 mg.

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