INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Structure Biosynthesis And Examination Of Bioactive Small Molecule

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ARTICLE INFO

Received: 22 Jan 2024
Accepted: 26 Jan 2024
Published: 06 Feb 2024
Keywords:
Bioactive Small Molecule, Structure Biosynthesis.
DOI:
10.5281/zenodo.10625232

ABSTRACT

Collaborative research projects between chemists, biologists, and medical scientists have inevitably produced many useful drugs, biosensors, and medical instrumentation. Organic chemistry lies at the heart of drug discovery and development. The current range of organic synthetic methodologies allows for the construction of unlimited libraries of small organic molecules for drug screening. In translational research projects, we have focused on the discovery of lead compounds for three major diseases: Alzheimer disease, breast cancer, and viral infections. In the Alzheimer disease project, we have taken a rational-design, approach and synthesized a new class of tricyclic pyrone compounds that preserve memory and motor functions in amyloid precursor protein /presenilin-1 mice. TP's could protect neuronal death through several possible mechanisms, including their ability to inhibit the formation of both intraneuronal and extracellular amyloid B aggregates, to increase cholesterol efflux, to restore axonal trafficking, and to enhance long-term potentiation and restored LTP following treatment with amyloid B Oligomers.

INTRODUCTION

This Personal Account describes three translational research projects that were carried out in our laboratories that involved the discovery of bioactive compounds or lead compounds for the treatment of Alzheimer disease, breast cancer, and viral infections. About 35 million. people worldwide suffer from AD and the currently available treatments for Alzheimer disease, such as donepezil, rivastigmine, galantamine, and memantine, temporarily ameliorate some of the symptoms but do not modify the underlying disease. As such, there is an urgent need and challenge for the discovery of new drugs that treat this disease. We have discovered a newclass of tricyclic pyrones that possess high oral bioavailability, excellent permeability through the blood/brain barrier, and low toxicity; these pyrones substantially decrease the number of soluble and insoluble amyloid betaspecies in the

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

brain and preserve memory and motor functions in Alzheimer disease transgenic mice. Tumor cells have impeded or altered cell-to- cell communication, one type of cell-cell communication is through a gap junction. We synthesized a library of substituted quinolines and found that several compounds possessed potent inhibitory activity against T47D breast cancer cells through the enhancement of gap- junctional intercellular communication (GJIC); these compounds reduced xenografted breast tumors in mice and completely eradicated tumor formation in spontaneous transgenic mammary mice. Viral infections, including influenza, are responsible for over 3 million cases of illness and up to half a million deaths per year. Although antiviral drugs against certain viral infections are available, the emergence of viral resistance to existing antiviral drugs.

ORAL DRUG DESIGN

FORMULATION OF FLOATING BIOADHESIVE TABLET

Effervescent floating-Bioadhesive tablet batches were prepared by direct compression method. Rivastigmine, Carbopol and hydroxy propyl methyl were sieved through # 30 sieve, and microcrystalline cellulose (filler), NaHCO (sodium hydrogen carbonate), (12%) and Magnesium Stearate (1%) were sieved through # 60 sieve prior to use. The amount of rivastigmine hydrogen tartarate (equivalent to 12 mg base) was kept as constant in each formulation. All the materials were accurately weighed and blended using a hand blender, and subsequently compressed on a manual single punch tablet compression machine (M/s Cadmach Industries, Ahmedabad, India) into 100 mg tablets using flat-faced, round punches 8 mm in diameter (batch size per formulation composition was 100 tablets).

Selection of polymer

During preliminary studies, five polymers viz. CP971P, PEO 301, sodium carboxy methyl cellulose C, HPMC KIOOLV and HPMC KISM CR were chosen for formulating oral CR floating-bioadhesive matrices of rivastigmine. Tablets were prepared using blends of these polymers, with the ratios of rivastigmine to polymer kept as 1:4. Subsequently depending upon the results obtained, polymer blend (PB) containing only two polymers, CP 971P and HPMC KISM CR. was selected for further investigation.

TRANSDERMAL DRUG DESIGN

Material

RVS sample was obtained from Sodhana Laboratories, Hyderabad, India. DURO-TAKTM adhesives 87-900A, 87-4098, 87-2510 and 87 9301 were obtained from Henkel Corporation, USA. Release liner (9742 Scotchpak) and backing membrane (9722 Cotran) were obtained from 3M, USA Armumonium acetate, water and methanol of HPLC grade were purchased from E.Merck, Mumbai, India. Sodium chloride was purchased from SDFCL, Mumbai, Indi.

Preparation of 0.9% NaCl solution

Method

0.9g of Sodium chloride was weighed accurately and transferred to clean dry volumetric flask containing 50ml of HPLC grade water, made to dissolve and then the volume was adjusted to 100ml with the same. The prepared saline solution was sonicated before use.

Preparation of transdermal patches.

The DIA transdermal patches were prepared as per formulae given in Table 1. R VS was dissolved dispersed in adhesive and the resulting mixture was sonicated for 10 min and cast on the release liner (9742 Scotch Pak, 3M USA) with a wet film applicator Paul N. Gardner Company Inc, USA) set at 30 mil thickness and was kept at room temperature for 30min and dried at 70 0C or 5min.

Structure of Rivastigmine

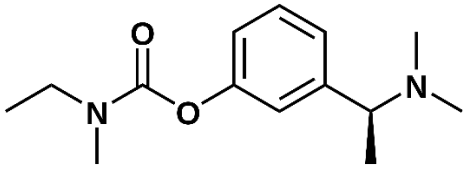

Fig No. 1: Rivastigmine

Molecular formula

($C_{14}H_{22}N_20_2$)

IUPAC Name

3-[(1S)-1-(dimethylamino)ethyl]phenyl N-ethyl-N-methylcarbamate

Mechanism of action Rivastigmine

Rivastigmine is a cholinesterase inhibitor used in the treatment of Alzheimer's disease and Parkinson's disease. It works by inhibiting acetylcholinesterase, an enzyme that breaks down acetylcholine in the brain. By inhibiting this enzyme, rivastigmine increases the levels of acetylcholine, a neurotransmitter involved in learning and memory. This enhancement of acetylcholine levels is thought to temporarily improve cognitive function in individuals with these neurodegenerative disorders.

Uses

Alzheimer's Disease: Rivastigmine is used to alleviate cognitive symptoms in individuals with mild to moderate Alzheimer's disease. It may help improve memory, attention, and the ability to perform daily activities Parkinson's Disease Dementia: In cases where dementia is associated with Parkinson's disease, rivastigmine is used to manage cognitive impairments. It can be beneficial in improving cognitive function and quality of life in these patients.

Adverse effects

1. Gastrointestinal Disturbances: Nausea, vomiting, diarrhea, and abdominal pain are among the most frequently reported side effects.
2. Central Nervous System Effects: Headache, dizziness, and fatigue may occur.
3. Skin Reactions: Skin irritation or redness at the application site for transdermal patches) may occur.
4. Musculoskeletal Effects: Some individuals may experience muscle weakness.

Pharmacodynamics

The pharmacodynamics of rivastigmine primarily involves its action as a cholinesterase inhibitor, it affects the cholinergic system in the central nervous system. Here are key points related to the pharmacodynamics of rivastigmine Cholinesterase Inhibition: Rivastigmine inhibits acetylcholinesterase, an enzyme responsible for breaking down acetylcholine in the synaptic cleft. By inhibiting this enzyme, rivastigmine increases the concentration and duration of action of acetylcholine. Enhancement of Cholinergic Transmission: The increased levels of acetylcholine in the brain, particularly in areas related to memory and cognitive function, can temporarily improve cholinergic neurotransmission. This is especially relevant in conditions like. Alzheimer's disease, where a deficiency of acetylcholine is observed Effect on Cognitive Function: By modulating cholinergic neurotransmission, rivastigmine aims to mitigate cognitive decline associated with Alzheimer's disease and Parkinson's disease dementia, improved cholinergic function may contribute to enhanced memory and cognitive abilities. Transdermal Formulation: In addition to oral administration, rivastigmine is available in a transdermal patch form. This formulation provides a continuous and controlled release of the medication, offering a more stable and sustained effect.

Pharmacokinetics

The pharmacokinetics of Rivastigmine involves the processes of absorption, distribution, metabolism, and elimination within the body. Here's an overview:

1. Absorption

Rivastigmine is well absorbed after oral administration. It can be administered orally in capsule Or solution form Absorption occurs primarily in the gastrointestinal tract. Rivastigmine is distributed widely in body tissues, including the central nervous system.

2. Distribution

Crosses the blood-brain barrier, allowing it to exert its effects within the brain.

3. Metabolism

Metabolism of rivastigmine occurs primarily in the liver. The major metabolite is the Decarbamylated metabolite, NAP226-90. Both rivastigmine and its metabolites are excreted in Urine.

4. Elimination

The elimination half-life of rivastigmine is relatively short, approximately 1-2 hours. Rivastigmine and its metabolites are primarily excreted in the urine.

EVALUATION OF TABLET

1. Weight Variation test:

Take 20 tablet and weighed individually. Calculate average weight and compare the individual tablet weight to the average. The tablet pass the U.S.P. test if no more that 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

2. Content Uniformity Test:

Randomly select 30 tablets. 10 of these assayed Individually. The Tablet pass the test if 9 of the 10 tablets must contain not less than 85% and not more than 115% of the labeiled drug content and the 10th tablet may not contain less than 75% and more than 125% of the labelled content. If these conditions are not met, remaining 20 tablets assayed individually and none may fall outside of the 85 to 115% range.

3. Dissolution Test (U.S.P.) Apparatus 1:

A single tablet is placed in a small wire mesh basket attached to the bottom of the shaft connected to a variable speed motor. The basket is immersed in a dissolution medium (as specified in monograph) contained in a 100 ml flask. The flask is cylindrical with a hemispherical bottom. The flask is maintained at 37±0.5°C by a constant temperature bath. The motor is adjusted to turn at the specified speed and sample of the fluid are withdrawn at intervals to determine the amount of drug in solutions,

4. Disintegration Test:

The U.S.P. device to test disintegration uses 6 glass tubes that are 3 long, open at the top and 10 mesh screens at the bottom end. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at 37:20 C such that the tablet remains 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. Move the basket containing the tablets up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet. According to the test the tablet must disintegrate, and all particles must pass through the 10-mesh screen in the time specified. If any residue remains, it must have a soft mass. Disintegration time: Uncoated tablet: 5-30 minutes Coated tablet: 1-2 hour

Non-Official test tablet

1. General Appearance:

The general appearance of a tables, its visual identity and overall "elegance is essential for consumer acceptance, for control of lot-to-lot uniformity. Appearance of a tablet involved the measurement of a tablet's shape, Color, odour.

a. Organoleptic Properties:

Many pharmaceutical tablets use color as a vital means of rapid identification and consumer acceptance. The color of a product must be uniform within a single tablet.

b. Size & Shape - Measured by:

Micrometer. Tablet thickness should be controlled within 25% variation of standard value. More likely to cause capping problems.

2. Hardness:

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand Mechanical shocks of handling in manufacture, packing and shipping. Hardness thus sometimes termed the tablet crushing strength.

Tablet hardness tester are: -

- Monsanto tester
- Pfizer tester.
- Strong cobb tester
- Erweka tester
- Scleuniger tester

3. Friability

The friability test is official in USP but not in BP and IP Friability tester is known as the Roche friabilator. Tablet hardness is not an absolute indicator of strength since some formulations, when compressed into very hard tablets.

EVALUATION TEST OF TRANSDERMAL PATCH

A. Physicochemical Evaluation
B. In Vivo Evaluation.
C. In Vitro Evaluation

A. Physicochemical Evaluation

Interaction studies are taken out by Thermal analysis, FTIR, UV and chromatographic techniques by

Interaction study comparing their physicochemical properties like assay, melting. point, wave numbers, absorption maxima.

Thickness of the patch:

The thickness of the drug prepared patch is measured by using a digital micrometer at different point of patch and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

Weight uniformity:

The prepared patches are to be dried at 60°c for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Drug content:

A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyse the drug contain with the suitable method (UV or HPLC technique).

Percentage elongation break test:

Elongation percentages 4x100 Where, L. Las is the final length of each strip. La is the initial length of each strip.

Probe Tack test:

In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive, and when a bond is formed between probe and adhesive. The subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams.

Stability studies:

Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at 40±0.5°c and 7545% RH for 6 months. The samples were withdrawn at 0, 30, 60, 90 and 180 days and analysed suitably for the drug content.

B. In Vitro Evaluation

The paddle over disc method (USP apparatus V) can be employed for assessment. of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed, and fixed over a glass. plate with an adhesive. The glass plate was then placed in a 500-ml. of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to 322 0.5°C. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5 ml aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC The experiment is to be performed in triplicate and the mean value can be calculated.

C. In Vivo Evaluation.

In vivo evaluations are the true depiction of the drug performance. The variables which cannot be taken into account during in vitro studies can be fully explored during in vivo studies. In vivo evaluation of TDDS can be carried out using Animal model and Human volunteers.

1. Animal model-

Considerable time and resources are required to carry out human studies, so animal studies are preferred at small scale. The most common animal species used for evaluating transdermal drug delivery systems are mouse, hairless rat, hairless dog, hairless rhesus etc. Rhesus monkey is one of the most reliable models for in vivo evaluation of transdermal drug delivery in animals.

2. Human model-

The final stage of the development of a transdermal device involves collection of pharmacokinetic and pharmacodynamic data following application of the patch to human volunteers. Clinical trials have been conducted to assess the efficacy, risk involved, side effects, patient compliance etc. Phase I clinical trials are conducted to determine mainly safety in volunteers. Phase II clinical trials determine short term safety and mainly effectiveness in patients. Phase III trials indicate the safety and effectiveness in large number of patient population, phase IV trials at post marketing surveillance are done for marketed patches to detect adverse drug reactions. Human studies require considerable resources, but they are the best to assess the performance of the drug.

CONCLUSION

Rivastigmine may only have a mild to moderate effect on Pervasive developmental disorders. Tolerability is an issue (high dropout rates).

Worsening of parkinsonian symptoms. However, not much choices as of now since there are not many options for Pervasive developmental disorders. Rivastigmine is a useful option for the treatment of patients with mild to moderately severe Alzheimer's disease. Although only short term (6 month) comparisons with placebo are available, given the lack of established treatment options it should be considered for first line use in this population. Rivastigmine appears to be beneficial for people with mild to moderate Alzheimer's disease. In comparisons with placebo, improvements were seen in cognitive function, activities of daily living, and severity of dementia with daily doses of 6 to 12 mg. Adverse events were consistent with the cholinergic actions, of the drug Further research is desirable on dosage (frequency and quantity) in a search for ways to minimize adverse effects. This review has not examined economic data.

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HOW TO CITE: Pravin D. Chand, Prachi P. Udapurkar, A. S. Sanap, Structure Biosynthesis And Examination Of Bioactive Small Molecule, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 2, 139-144. https://doi.org/10.5281/zenodo.10625232