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NOVEL APPROACH FOR DESIGN AND CHARACTERIZATION OF MUCOADHESIVE BUCCAL GANCICLOVIR IN SITU GEL

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ABSTRACT

The present study was to designed to prepare periodontal gel of ganciclovir for the treatment of inflammation conditions. In this studyit was found that as the phospholipid concentration was increased, it resulted in corresponding increase in the entrapment efficiency of reconstituted liposomes. In conclusion, a sustained delivery of ganciclovir can be achieved by proliposomal drug delivery system. Phospolipids, being the major component of liposomal system, can easily get integrated with the skin lipids and maintain the desired hydtation conditions to improve drug permeation. Fusion of lipid vesicles with skin ontributed to the permeation enhancement effect. In-vitro studies concluded the enhance skin permeation and retention of Ganciclovir was observed and was due to liposolubilized state of drugs with in proliposomes which helped to produce the deport effect. The prepared proliposomes are incorporated into gel. The data show that liposomal systems can make the drug molecules more accessible with in skin layers. The conclusion compares favourably with early study showed that drug associated with liposomes bilayer bounds and better routed into skin. Other studies have shown that liposomal ambience may help modify the permimeability characteristics of the stratum corneum, and the system keep the drug molecules with in skin layers so that sustain release of drug can be achieved. The results advocate the extension of this worh on the preliminary clinical trails and commercialization of proliposomal gel formulation of antiviral drugs for effective buccal pharmacotherapy in treatment of virus.

KEYWORDS: Gancivlovir, Proliposomal gel.

INTRODUCTION

The unique environment of the oral cavity offers its potential as a site for drug delivery. Because of the rich blood supply and direct access to systemic circulation, the oral mucosal route is suitable for drugs, which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver (First pass effect).

The total area of the oral cavity is about 100cm.square.Out of this about one third is the buccal surface, which is lined with an epithelium of amount 0.5mm thickness. The oral mucosal surface is constantly washed by the saliva (Daily turn out is above 0.5 to 2 litres). The continuous secretion of saliva results in rapid removal of released drug. Conversely, the thin mucin film, which exists on the surface of the oral mucosa, may provide an opportunity to retain a drug delivery system in contact with the mucosa for prolonged periods if it is designed to be mucoadhesive. Such systems ensure a close contact with absorbing membrane, thus optimizing the drug concentration gradient across the biological membrane and reducing the differential pathway. Therefore, the buccal (oral) mucosa may be a potential site for controlled or sustained drug delivery.

Drug delivery via the membranes of the oral cavity is traditional divided into three categories,

- Buccal delivery, which infers drug administration through the lining of the cheek to the systemic circulation.
- Sublingual delivery, which infers drug administration through the administration of drug via membranes of the floor of the mouth for the systemic circulation.
- Local delivery to mouth, which involves treatment conditions within the oral cavity by administration to the effected mucosal tissues.

  These sites for delivery differ in both structure and composition as well as in degree of permeability and therefore, also vary in their ability to retain a deliver for a desired length of time.

Delivery through Buccal Mucosa

Administration of a drug via the buccal mucosa (the lining of the cheek) to the systemic circulation is defined as buccal delivery. Despite, the buccal mucosa is significantly less permeable than the sublingual mucosa and usually not able to provide rapid drug absorption or good bioavailability; it is relatively more permeable than the skin and also offers other advantage over alternative delivery routes. The fact that the buccal mucosa is less permeable

than sublingual floor makes it more desirable site for sustained drug delivery. Apart from avoiding enzymatic degradation and first pass metabolism, the non acidic conditions and lipophilic nature of the buccal tissue provide potential and promises for successful delivery of peptide and proteins.

The various strategies Employed for Buccal Delivery

- Bio adhesive Buccal Tablets
- Bio adhesive buccal Gels
- Bio adhesive Buccal Patches.

Bioadhesive Buccal Tablets

Bioadhesive tablets are immobilized drug delivery systems. They can be formulated into monolithic, partially coated or multi-layered matrices. Monolithic tablets are easy to manufacture by conventional techniques and provide for the possibility of loading large amount of drug. In case of bi-layered tablets, drug can be incorporated in the adhesive layer, which comes in contact with the mucosal surface. This drug containing mucoadhesive layer is then protected from the oral cavity environment by a super upper inert layer (backing layer), which faces into the oral cavity.

Bioadhesive Buccal Patches

Adhesive patches can be designed either for unidirectional release into the oral mucosa or for bi-directional release into the oral cavity as well as into the oral mucosa. The adhesive part of the system can be used as drug carrier or as an adhesive for the retention of a drug loaded non-adhesive layer. In this respect, a peripheral adhesive ring could be casted. The use of an impermeable backing layer will maximize the drug concentration gradient and prolong adhesion because the system is protected from saliva.

Bioadhesive buccal Gels

Viscous adhesive gels have been designed for local therapy using polyacrylic acid and polymethacrylate as gel forming polymers. Gels are reported to prolong residence time on the oral mucosa to a significant level. This not only improves absorption but also allows for sustained release of the active principle.

BUCCOADHESIVE DRUG DELIVERY

The potential route of buccal mucosal route of drug administration was first recognized by Walton and others reported in detail on the kinetics of buccal mucosal absorption.

Buccoadhesion, or the attachment of a natural or synthetic polymer to a biological substrate, is a practical method of drug immobilization or localization and an important new aspect of controlled drug delivery. The unique environment of the oral (buccal) cavity offers its potential as a site for drug delivery. Because of the rich blood supply and direct access to systemic circulation. The Buccal route is suitable for drugs, which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver (first pass effect).

Buccal route of administration: The medicament is placed between the cheek and the gum. The barrier to drug absorption from this route is the epithelium of oral mucosa. Passive diffusion is the major mechanism for absorption of drugs. Drugs with short biological half-lives, requiring a sustained effect, poor permeability, sensitivity to enzymatic degradation and poor solubility may be successfully delivered via bioadhesive buccal delivery systems.

Advantages of Buccal route: Rapid absorption and higher blood levels due to high vascularization of the region and therefore particularly useful for administration of antianginal drugs.

1. No first-pass hepatic metabolism.
2. No degradation of drugs such as that encountered in the GIT.
3. Presence of saliva facilitates both drug dissolution and its subsequent permeation by keeping the oral mucosa moist.
4. It is a safer method of drug administration, since drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity.

Disadvantages of buccal route

1. Accidental swallowing of the formulation by the patient.
2. Difficulty in speaking and drinking.

Limitations

1. Only limited amount of drug can be used in these systems (25-50 mg).
2. Drug must be non-irritant to the buccal mucosa.

Factors affecting systemic absorption of drugs through the buccal mucosa

There are several factors affecting the absorption of drugs through the buccal mucosa.

a) Biological factors

- Mucosal surface area
- Thickness of oral epithelium
- Structure of oral mucosa
- pH of environment
- Salivary secretion

b) Drug factors

- Solubility
- Biological half life
- Drug stability
- Rate of absorption

c) Formulation factors

- Size and shape
- Texture
- Properties of excipients
- Release characteristics
- Mobility of backing layer

In the past few decades, considerable attention has been focused on the development of new drug delivery system (NDDS). The NDDS should ideally fulfil two prerequisites. Firstly, it should deliver the drug at a rate directed by the needs of the body, over the period of treatment. Secondly, it should channel the active entity to the site of action. Conventional dosage forms including prolonged release dosage forms are unable to meet none of these. At present, no available drug delivery system behaves ideally, but sincere attempts have been made to achieve them through various novel approaches in drug delivery.[1] Approaches are being adapted to achieve this goal, by paying considerable attention either to control the distribution of drug by incorporating it in a carrier system, or by altering the structure of the drug at the molecular level, or to control the input of the drug into the bio environment to ensure an appropriate profile of distribution.

Novel drug delivery system aims at providing some control, whether this is of temporal or spatial nature or both, of drug release in the body. Novel drug delivery attempts to either sustain drug action at a predetermined rate or by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects. It can also localize drug action by spatial placement of controlled release systems adjacent to, or in the diseased tissue or organ or target drug action by using carriers or chemical derivatization to deliver drug to particular target cell type.

In recent years, vesicles have become the vehicle of choice in drug delivery. Lipid vesicles were found to be of value in immunology, membrane biology, diagnostic techniques, and most recently, genetic engineering.[2-4] Vesicles can play a major role in modelling biological membranes, and in the transport and targeting of active agents. Encapsulation of a drug in vesicular structures can be predicted to prolong the existence of the drug in systemic circulation and perhaps, reduces the toxicity if selective uptake can be achieved.[5] The phagocytic uptake of the systemic delivery of the drug loaded vesicular delivery system provides an efficient method for delivery of drug directly to the site of infection, leading to reduction of drug toxicity with no adverse effects.

Vesicular drug delivery reduces the cost of therapy by improved bioavailability of medication, especially in case of poorly soluble drugs. They can incorporate both hydrophilic and lipophilic drugs. These systems delay drug elimination of rapidly metabolizable drugs and function as sustained release systems and solve the problems of drug insolubility, instability and rapid degradation. Consequently, a number of vesicular delivery systems such as liposomes, transferosomes, pharmacosomes, niosomes or proniosomes etc, were developed.

PROLIPOSOMES

- Proliposomes are defined as dry, free flowing powder formulations containing water soluble carrier particles coated with phospholipids that immediately form a liposomal dispersion on contact with water in the body.[16] The resulting liposomes may act as a sustained release dosage form of the loaded drugs.
- Proliposomes are composed of drug, phospholipid and a water soluble porous powder and can be stored sterilized in a dried state. Because of the solid properties, the stability problems of liposome can be resolved without influencing their intrinsic characteristics.[18]

- Improvement of Solubility and bioavailability of poorly water soluble drugs.[17]

Advantages of proliposomes over liposomes

- The stability problem of liposomes can be resolved
- Sterilization is easy
- They immediately form liposomal suspension due to the presence of water soluble matrix (mannitol).
- For proliposomes to be used in cosmetics and skin care it is essential that they should have following properties.

1. Ability to be taken up in stratum corneum i.e., horny layer of epidermis
2. Ability to penetrate the horny layer
3. Ability to exert an influence on the cellular metabolism of the living epidermis.

Materials used for proliposome formulation[18]

- ✓ phosphotidyl choline (vehicle forming agent)
- ✓ Cholesterol (prevent the leakaging from vesicles)
- ✓ Mannitol (water soluble porous solid matrix)
- ✓ Organic solvents (providing softness to vesicle membrane).

Preparation method[20]

Proliposomes were prepare by film depositon on carrier method using rotary evaporator. Naproxen proliposomes were prepared by the penetration of a chloroform-methanol solution of naproxen, cholesterol and phsphotidyl choline into microporous, water soluble carrier (mannitol) with subsequent drying. Mannitol (1 g, sieved with 100 mesh) was placed in 100ml round bottom flask which was held at 60-70^{0}C temperature and the flask rotated at 80-90 rpm for 30 min under vacuum. After complete drying the temperature of water bath was lowered to 20-30^{0}C. naproxen (10 mg), phosphotidyl choline and cholesterol were dissolved in mixture of organic solvents (chloroform:methanol, 6:4,v/v) and 5ml of aliquot of organic solution was slowly introduced into the flask via the solvent inlet tube. After complete drying second aliquot (5ml) was introduced. After complete drying, the vacuum was released and proliposomes were placed in a desiccator over night and then sieved with 100mesh.

Compared with mannitol, the appearance of the proliposomes was viscous using sodium chloride and sorbitol as carrier. As a result, mannitol was selected as the carrier for proliposomes.

In-Vitro drug release

These studies are conducted by using dialysis membrane over franz diffusion cell. 1gm gel is taken on dialysis membrane and is placed between receptor and donor compartment filled with 30ml 7.4 P^H phosphate buffer. The franz diffusion cell is placed over magnetic stirrer with 100 rpm and temperature is maintained at 37 ± 1^0c. 5 ml of samples are withdrawn periodically and replaced with fresh buffer. The withdrawn samples are appropriately diluted and analysed for drug content.

Stability studies

Stability studies are carried out by storing the prepared provesicles at various temperature conditions like refrigiration temperature ($2\text{-}8^0$c), room temperature (25 ± 0.5^0c) and elevated temperature (45 ± 0.5^0c) from period of one month to 3 months. Drug content and variation in the average vesicle diameter are periodically monitored.

AIM AND OBJECTIVES

AIM

To prepare and evaluate Ganciclovir insitu proliposomal gel for perioral drug delivery using suitable materials and evaluated by proper test procedures. The prepared proliposomes are incorporated into gels.

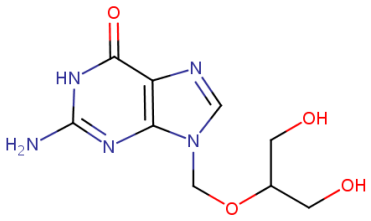
OBJECTIVE

1. To develop an effective insitu proliposomal gel formulations.
2. Characterization of mannitol, lecithin and gellan gum with respect to their physicochemical properties.
3. Analytical method development for proliposomal formulation.
4. Drug and excipient compatibility studies using FTIR.
5. Optimization of the selected formulation based on the vesicle size and Entrapment efficiency.
6. Characterization and determination of proliposomal gel formulation for topical drug delivery.
7. Stability studies as per ICH guidelines Q1.
8. In vitro evaluation of the effectively developed proliposomal gel formulation.

DRUG AND EXCIPIENT PROFILE

- **Drug name : GANCICLOVIR**

- **Iupac name** : 2-amino-9-{[(1,3-dihydroxypropan-2-yl)oxy]methyl}-6,9-dihydro-1H-purin-6-one.
- **Synonyms** : Ganciclovir, GA2, 9-[(1,3-dihydroxy-2-propoxy)methyl]guanine,
- **Solubility** : Soluble in 0.1 M HCl (10 mg/ml), DMSO (5 mg/ml), water (2 mg/ml), hot methanol, and ethanol (<1 mg/ml).
- **Description** : An acyclovir analog that is a potent inhibitor of the Herpesvirus family including cytomegalovirus. Ganciclovir is used to treat complications from AIDS-associated cytomegalovirus infections.
- **Melting point** : 250°C
- **CAS NO** : 82410-32-0
- **Structure** :



- **Molecular formula** : $C_9H_{13}N_5O_4$
- **Molecular weight** : Average: 255.2306 Monoisotopic: 255.096753929 g/mol.
- **Bioavailability** : 5% (oral)
- **Half-life** : 2.5 to 3.6 hours
- **Protein binding** : 1 to 2%
- **Dosage forms** : injection, gel, poeder, capsule.
- **Dose** : 250,500mg. 500mg/10ml.
- **Category** : Antiviral Agents

MATERIALS AND METHODOLOGY

Materials Used

The following materials are used for project work

S.No.	Materials	Source
1	Ganciclovir	A gift sample from Dr.Reddy's laboratories, Hyderabad. AP.
2	Mannitol	SD Fine-Chem. Pvt., Mumbai, India.
3	Cholesterol	SD Fine-Chem. Pvt., Mumbai, India.
4	Phosphotidyl choline	Dr. Reddy's laboratories, Hyderabad, AP.
5	Chloroform	Merk laboratories, Mumbai
6	Methanol	Merk laboratories, Mumbai
7	Gellan gum	Yaro chemicals, Mumbai
8	Triethanolamine	Fisher scientific, Mumbai

List of chemicals used with supplier

Instruments Used

S.No.	Instrument name	Manufacturer	Model
1	UV spectrophotometer	Lab India	32000
2	Rota evaporator	Helidopath	Sonics-569-00050-00-0
4	Optical microscope	Metzer	5000DTM
5	Viscometer	Brook field	LVDV II pro+
6	Magnetic stirrer	Remi	1ML
7	Zeta sizer	Malvern	
8	Hot air oven	Navtug	D5247
9	Weighing balance	Shimadzu	Apx224
10	Water purifier	Labindia	SGLABOSTAR3TWF
11	Scanning electron microscope		
12	P^H meter	Lab India	SAB 5000
13	FTIR	Brucker	Alpha-T
14	KBR Pellet Press	Horizon	WC-56
15	Ultra Sonicator	Citizen	CD4520
16	Cooling centrifuge	REMI	TR-01
17	Homogenizer	REMI	RQT-124A

List of equipments used

METHODOLOGY

Preformulation studies

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It is the first step in the rational development of dosage forms.

Objective

The overall objective of preformulation testing is to generate information useful to the formulation in developing stable and bioavailable dosage forms.

Scope

The use of preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product.

Melting point determination

Melting point of Ganciclovir was set to determine by open cup capillary method.

Analytical Method Development

Determination of absorption maxima

Absorption maxima is the wavelength at which maximum absorption takes place. For accurate analytical work, it is important to determine the absorption maxima of the substance under study.

Procedure

For the preparation of calibration curve stock solution was prepared by dissolving 100 mg of accurately weighed drug in 100ml of methanol (1mg/ml). Further 1ml of the stock solution was pipette out into a 100 ml volumetric flask and volume was made up with phosphate buffer (7.4 PH). From this stock solution pipette out 1ml and dilute to 10 ml with phosphate buffer and subject for UV scanning in the range of 200-400 nm using double beam UV spectrophotometer. The absorption maxima was obtained at 270 nm with a characteristic peak.

Preparation of calibration curve

Using absorption maxima a standard curve was prepared in the concentration range of 0.5-2.5 µg/ml. from the second stock solution, pipette out 0.5, 1.0, 1.5, 2.0 and 2.5 ml into a series of 10ml volumetric flask and volume was made up to 10 ml with phosphate buffer PH 7.4 to get 0.5, 1.0, 1.5, 2.0 and 2.5 µg/ml of Ganciclovir respectively. The absorbance of resulting solutions were measured at 270nm and recorded. Concentration versus absorbance values were plotted.

Drug-excipients interaction studies by FTIR

The compatibility between pure drug and mannitol, phosphatidyl choline, cholesterol were detected by FTIR (Bruker Alpha- T) spectra. The potassium bromide pellets were prepared on KBR press (Horizon WC-56). To prepare the pellets the solid powder sample were ground together in a mortar with 100 times quantity of KBR. The finely grounded powder introduced into a stainless steel die. The powder was pressed in the die between polished steel anvils at a pressure of about $10t/in^2$. The spectra's were recorded over the wave number of 4000 to 600 cm^{-1}.

Preparation of proliposomal gel

Preparation of Ganciclovir loaded proliposomes

Proliposomes could be prepared by many methods including

a. Film deposition on carrier method
b. Crystal film method
c. Fluidized bed method
d. Powder bed grinding method
e. Freeze drying method
f. Spray drying method.

Based on the laboratory conditions film-deposition on the carrier method was chosen to prepare Ganciclovir proliposomes.

- Variables for optimization of proliposomes:

➢ Mannitol
➢ Phosphatidyl choline
➢ Cholesterol.

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