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Formulation and Evaluation of Glimepiride Sublingual Tablets

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***Abstract*: Oral mucosal delivery of drugs promotes rapid absorption and high bioavailability, with a subsequent immediate onset of pharmacological effect. However, many oral mucosal deliveries are compromised by the possibility of the patient swallowing the active substance before it has been released and absorbed locally into the systemic circulation. The aim of this research was to introduce a new glimepiride formula for sublingual administration and rapid drug absorption that can be used in an emergency. Sublingual tablets of glimepiride can be successfully prepared by direct compression method using selected superdisintegrants with Crosspovidone 1.5%, 3%, 6%, Crosscarmellose 1.5%, 3%, 6% and Sodium starch glycolate 1.5%, 3%, 6%, for the better patient compliance and effective therapy the relative efficiency of these superdisintegrant to improve the disintegration and dissolution rate of tablets were found in order. Crosspovidone shows good result as compare to other superdisintegrants. Crosspovidone>crosscarmellose sodium > sodium starch glycolate.**

***Keywords*: Glimepiride Sublingual Tablets**

1. Introduction

Formulation development involves a great deal of study and experimental methods to get optimum results. While doing so we have to consider various factors like choice of excipients, bioavailability of drug, drug stability, cost effectiveness, manufacturing aspects.

Nowadays drugs can be delivered with a convenience manner, performance and bioavailability. Drugs have been applied to the mucosa for topical application since many years. However, recently there has been interest in exploiting the oral cavity as a portal for delivering drugs to the systemic circulation.

The Drug delivery through sublingual route have desire to provide quick onset of pharmacological effect. Dysphasia (difficulty in swallowing) is a common problem of all age groups, especially elderly, children, and patients who are mentally retarted, un cooperative, nauseated or on reduced liquid- intake/diets have difficulties in swallowing these dosage forms. Sublingual administration of the drug means placement of the drug under the tongue and drug reaches directly into the blood stream through the ventral surface of the tongue and bottom of the mouth.

The sublingual route usually produces a faster onset of action than the orally ingested tablets and the portion absorbed through the sublingual blood vessels by passes the hepatic first-pass metabolic processes.

A. Oral Mucosa

The oral cavity comprises the lips, cheek, tongue, hard palate, soft palate and floor of the mouth. The lining of the oral cavity is referred to as the oral mucosa, and includes the buckle, sublingual, gingival, palatal and labial mucosa. The oral mucosa top quarter to one-third is made up of closely compacted epithelial cells. The main role of the oral epithelium is to protect fluid loss and underlying tissue against potential harmful agents in the oral environment. Beneath the epithelium is the basement membrane, lamina propia and submucosa. The oral mucosa also having many taste receptors of the tongue and sensory receptors. The lining mucosa is found in the outer oral vestibule (the buckle mucosa) and the sublingual region (floor of the mouth) The specialized mucosa is found on the dorsal surface of tongue, while the masticatory mucosa is found on the hard palate (the upper surface of the mouth) and the gingiva (gums). The lining mucosa comprises approximately 60%, the masticatory mucosa approximately 25%, and the specialized mucosa approximately 15% of the total surface area of the oral mucosal lining in an adult human. The masticatory mucosa is located in the regions particularly susceptible to the stress and strains resulting from masticatory activity.

The superficial cells of the masticatory mucosa are keratinized, and a thick lamina propia tightly binds the mucosa to underlying periosteum. The mucosa of the dorsum of the tongue is specialized gustatory mucosa's, which has a well papillae surface; which are both keratinized and some non-keratinized5.

Whereas keratinized regions contain predominantly neutral lipids (creaminess). Non-keratinized areas are composed of glycosylceramides that appears to be derived from membrane coating granules that differ morphologically from the lamellate membrane coating granules of keratinized tissue.

The amount of a certain drug absorbed through the oral mucosa is determined by many factors, including the pKa of the base, the rate of partition of the unionized form of the drug, the lipid – water partition coefficient of that particular drug, and lastly, on the pH of the solution.

B. The oral mucosal cavity, delivery of drugs is classified into three categories

- Sublingual delivery: which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth.
- Buccal delivery: which is drug administration through the mucosal membranes lining the cheeks (buckle mucosa), and
- Local delivery: which is drug delivery into the oral cavity.

C. Advantages

- Rapid onset of effect - particularly for pain, emesis, insomnia or allergy relief.
- Easy, painless and convenient self-administration.
- To get pharmacological effect with less drugs, less side effect.
- Inexpensive to manufacture per dose.
- Flexible formulation options.
- The blood supply is rich with a capillary network close to mucosa6
- To easy administration such as geriatric, pediatric and psychiatric patients.
- A relatively rapid onset of action can be achieved compared to the oral route, and the formulation can be removed if therapy is required to be discontinued.
- Due to more contact surface area of oral cavity it provide good absorption.
- Liver is bypassed and also drug is protected from degradation due to pH and digestive enzymes of the middle gastrointestinal tract.
- They also present the advantage of providing fast dissolution or disintegration in the oral cavity, without the need for water or chewing.

D. Disadvantages

- It is difficult to convert a high dose poorly compressible API into a tablet of suitable size for human use.
- Difficult to formulate a drug with poor wettability, slow dissolution into a tablet.
- To show Slow onset of action as compared to parenterals, liquid oral form and capsules.
- Patients cannot be undergoing radiotherapy swallow tablet.

E. Sublingual Absorption

Sublingual, meaning literally 'under the tongue' refers to a method of administering substances via the mouth in such a way that the substances are rapidly absorbed via the blood vessels under the tongue rather than via the digestive tract.

However, not all substances are permeable and accessible to oral mucosa. Sublingual drug administration is applied in the field of cardiovascular drugs, steroids, some barbiturates and enzymes. It has been a developing field in the administration of many vitamins and minerals which are found to be readily and thoroughly absorbed by this method. Sublingually absorbed nutrition, which avoids exposure to the gastric system and liver, means direct nutritional benefits, particularly important for sufferers of gastro-intestinal difficulties such as ulcers, hyperactive gut, coeliac disease, and digestion, the elderly and invalids the nutritional advantage is independent of gastro-intestinal influences. Examples of drugs administered by this route include antianginal like nitrites and nitrates, anti-hypertensive like nifedipine, analgesics like morphine and bronchodilators like fenoterol. Certain steroids like estradiol and peptides like oxytocin can also be administered e.g. fentanyl citrate, apomorphine, prochlorperazinedimaleate (PRO), and hydrazine HCl8, 6. Glyceryltrinitrate one of the best used regularly it is rapid symptomatic relief of angina and potent coronary vasodilator. It has been found impressively effective when administered sublingually; pharmacologically active after only 1 – 2 minutes. The rapid relief of symptoms an aerosol spray was found due to first pass metabolism. The extent of first pass metabolism when compare to sublingual spray decreased to 48% with sublingual tablets and 28% with oral dose. Following sublingual administration, nitrates après in plasma concentrations can be maintained 24 hours.

2. Formulation of sublingual tablets

The formulation of sublingual tablets involves the selection of suitable excipients of bland taste that shall ultimately resulting in a rapid disintegrating tablet their by enhancing the dissolution of active ingredient. There are two different types of sublingual Tablets.

A. Molded Sublingual Tablets
B. Compressed Sublingual Tablet

1) Molded Sublingual Tablets

The sublingual tablets are usually prepared from soluble ingredients so that the tablets are completely and rapidly soluble. They contain, in addition of drug, excipients or base namely lactose, dextrose, sucrose, Mannitol. This tablet shows the same bioavailability as conventional tablets but has the advantage of markedly improved stability.

2) Compressed Sublingual Tablets

The compressed sublingual tablets are speed of absorption and a correspondingly rapid physiological response, which are normally best achieved with a rapidly soluble. Compressed sublingual tablets can be prepared by two different methods:

a. Wet Granulation Method
b. Direct Compression Method.

3) Wet Granulation Method

The excipients and drugs to get uniform mixture to passed through particular sieve. Suitable granulating agents like water, starch paste, providence can be added to the powder mixture in the appropriate proportion to produce a coherent mass. This mass is passed through a suitable sieve and dried at optimum temperature and sieved to get uniform granules. Then the

granules are lubricated and compressed into a tablet.

B. Direct Compression Method

The term direct compression is used to define a process by which tablets are compressed directly from the powder blends of active ingredients and suitable excipients, which will flow uniformly into the die cavity and compact. The great advantage of direct compression is the manufacturing cost. It uses conventional equipment, commonly available excipients, and a limited number of process steps. Direct compression is the easiest way to manufacture tablets and also fast melting tablets.

C. Freeze drying / lyophilization

Lyophilization is used to prepare tablets that have porous open matrix network

into which saliva rapidly disperses when placed in mouth. The drug is incorporate in a matrix water soluble which is freeze dried to make a unit which rapidly disperses when take in mouth. Apart from the matrix and active constituents, the final formulation may contain other excipients, which improve the process characteristics or enhance the quality of the final product. These include suspending agents, wetting agents, preservatives, antioxidants, colours and flavours. The preferred drug characteristics for freeze drying formulations are water in solubility, low dose, chemically stable, small particle size. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability.

D. Sublimation

Sublimation technique is addition of a volatile salt to the tabletting component,

mixing the components to obtain a substantially homogenous mixture and volatizing salt. The removal of volatizing salt creates pores in the tablet, which help in achieving rapid disintegration when the tablet comes in contact with saliva. The tablets were then subjected to vacuum at 80º C for 30 minutes to eliminate volatile components and thus create pores in the tablet. Volatile salts such as camphor, ammonium bicarbonate, naphthalene, urea, etc., were also used as sublimable components to prepare porous.

E. Spray drying

Spray drying produces highly porous and fine powder as the processing solvent is evaporated during process. Spray dryers are widely used in pharmaceuticals and biochemical process. Spray drying can be used to prepare rapidly disintegrating tablets by using support matrix such as hydrolyzed an non hydrolyzed gelatin and other components like Mannitol as bulking agent, sodium starch glycolate, Crosscarmellose sodium as disintegrants, acidic material like citric acid and alkali like sodium bicarbonate to enhance disintegration and dissolution13.

F. Mass Extrusion

This technology involves softening of the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into segments using heated blade to form tablets. The dried cylinder can also be use to coating granules of bitter tasting drugs and there by masking bitter taste.

3. Mechanism of super disintegrants

There are four main mechanisms for tablets disintegration as follows

1) Swelling

The most accepted general mechanism of action for tablet disintegration is swelling. The tablets with high porosity nature show poor disintegration due to have lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. Note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

2) Porosity and capillary action (Wicking)

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. The water up take by tablet mainly depends upon hydrophilicity of the drug/excipients and tableting conditions.

3) Disintegrating particle/particle due to repulsive forces

The another mechanism of tablet disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. Particle repulsion theory based on the observation that non swelling particle also cause disintegration of tablets. Water is required for The electric repulsive forces between particles are the mechanism of disintegration. Wicking is secondary.

4) Due to deformation

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. The swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet.

4. Summary and conclusion

A. Summary

The aim of the present study was to develop and optimize oral sublingual tablets of model drug (Glimepiride) to give quick onset of action by rapidly disintegrating in a few seconds without the need of water with better patient compliance. In such cases, bioavailability of drug is significantly greater and adverse event is reduced than those observed from conventional

tablet dosage form.

B. The work done is summarized as follows

By performing compatibility studies by IR spectrophotometry, no interaction was confirmed.

Oral disintegrating tablets were formulated by direct compression method and suitable analytical method based on UV-Visible spectrophotometer was developed for the model drug. Standard calibration curve prepared to determine the drug content in the prepared tablets and UV analysis was performed to determine the drug during in vitro release studies. Prior to compression, the blend of drug and excipients were evaluated for flow properties such as Angle of repose, loose bulk density, Tapped density, % Compressibility, and Hausner's ratio. All the formulations showed good flow properties.

Sublingual tablets were prepared by direct compression technique using CADMACH 16 station tablet punching machine, equipped with flat round punch of 8.7 mm diameter. Post compression evaluation of prepared sublingual tablets were carried out with the help of different pharmacopoeial and non pharmacopoeial (industry specified) tests. The shape and colour of all the formulations were found to be circular and white in colour. The thickness was found to be uniform in specific formulations. The hardness and friability are also within the permitted limits.

5. Conclusion

Sublingual tablets of glimepiride can be successfully prepared by direct compression method using selected superdisintegrants with Crosspovidone 1.5%, 3%, 6%, Crosscarmellose 1.5%, 3%, 6% and Sodium starch glycolate 1.5%, 3%, 6%. Crosspovidone shows good result as compare to other superdisintegrants. Crosspovidone > crosscarmellose sodium > sodium starch glycolate.

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