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PASTILLES: A NOVEL APPROACH IN DRUG DELIVERY SYSTEM- A REVIEW

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Abstract: Pastilles are the type of drug formulation that has normally a different course of administration through the buccal mucosa for drug delivery. These pastilles tend to help drug directly enter into the systemic circulation escaping hepatic first pass metabolism. This method of drug delivery is considered beneficial for enhancing the bioavailability of drugs. It is important to prepare oral formulation that enhance patience compliance, improve the administration and ensure the effectiveness of drug molecule. Pastilles act by slow dissolution rate in the oral cavity and are easy to administer. Pastilles are effective alternative to various dosage forms for their versatility and extended residence time in the oral cavity. This type of formulation allows an accurate dosage of drug, while enabling the patients to maintain the retention time of the drugs in the oral cavity. Pastilles have bright future as a novel and advanced method of drug delivering for local action and systemic affect in the oral cavity. This present article describes the effectiveness of the pastilles over other buccal dosage form. This review is a thorough study to apprehend the procedures involved in assessment of pastilles and the modern approach towards this type of drug delivery. This article intends to analyze the overall profile of pastilles and scope of future advances.

IndexTerms: Pastilles; Buccal Mucosa; Bioavailability; Retention Time; Versatility.

Introduction

Drug delivery through oral cavity

Oral route is preferred mostly to deliver therapeutic molecules because of its convenient administration and less expensive. This oral route has few problems like gastric degradation of drug, elimination and metabolism of drug molecules before systemic absorption. This biotransformation leads to inactive and toxic metabolites or breakdown products formation with low bioavailability (Chien et al., 1995). From the past ten years research is focused on intraoral drug delivery system for optimum therapeutic effect. The intraoral region is convenient for administration and will have fast therapeutic action. The intraoral mucosal routes have various advantages like bypassing hepatic metabolism and improving systemic oral bioavailability.

Structure and types of mucosa in oral cavity

The inner side of oral cavity consists of lips, soft palate, hard palate, cheek, tongue, and floor of mouth (Figure 1.1). The mucosal lining in oral cavity is present at, sublingual, palatal, gingival,buccal and labial areas. The oral epithelium's functional role is to protect tissue from harmful agents and fluid loss. Below the epithelium consists of basement membrane with 1-2 µm in thickness followed by *lamina Propria* and then submucosa (Shown in Figure 1.2). The oral mucosa present in tongue have sensory like taste receptors (Dowty et al., 1992).

The oral mucosa is of three types present in mouth. One is lining mucosa (approximately 60% of mouth surface area) mainly present at buccal mucosa and sublingual region (below tongue). Second is specialized mucosa (15% of mouth surface area) found on tongue dorsal surface and third is masticatory mucosa (approximately 25% of mouth surface area) found on hard palate and at gingival (Smart, 2004).

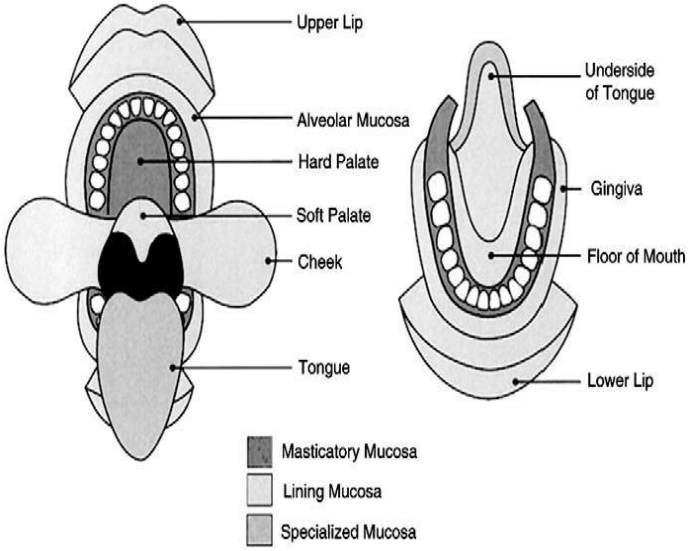

Fig 1.1: Different Parts and Mucosa types in Oral Cavity

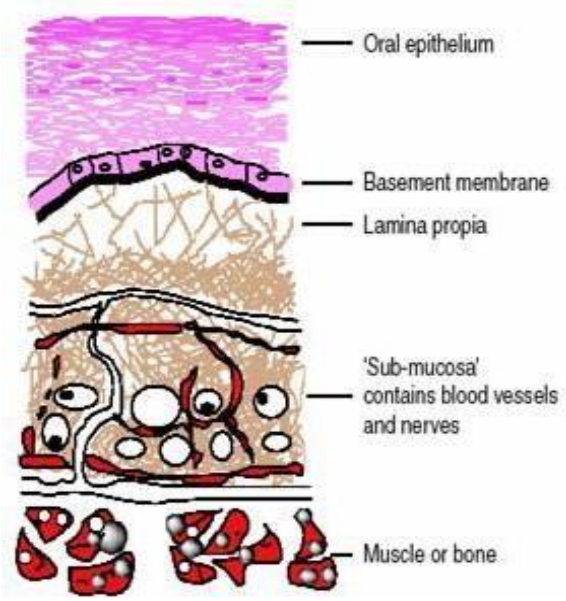

Fig 1.2: Cross-Section of Buccal Mucosa

The masticatory mucosa has keratinized epithelial cells and tightly binds to *lamina Propria*. The non-keratinized epithelium is present in lining mucosa and binds to thin elastic *lamina Propria* and submucosa. The keratinized and some non-keratinized epithelium are present in specialized mucosa at tongue dorsal surface (Collins, 1987)

Sites for administration in oral cavity

The mucosa present in oral cavity has different thickness and mucosal lining nature. The mucosa present in sublingual region of oral cavity lines at floor of mouth and have thinnest lining with more permeable in nature. This mucosal area has highly vascularized and sufficient surface area to get fast absorption and rapid onset of action. The constantly washed saliva in mouth and tongue makes difficult for dosage form to stay in contact with sublingual mucosa (Madhav et al., 2009). The oral buccal mucosa is present at inner side of cheek and used for local and systemic effect. Buccal mucosa have smooth surface with relatively immobile and highly permeable than other mucosal areas which is suitable for keeping controlled release dosage forms for longer time period. The soft palate is present at roof of oral cavity connecting to nasal parts of pharynx. This palatal mucosa is highly vascularised, very thin and has squamous epithelium.
Among all intraoral routes, buccal route have various advantages like easy to administer, convenient, localized and non-invasive in nature. Mostly buccal mucosa has highly vascularised blood vessels, highly permeable and lymphatic. Drugs administered through buccal mucosa enters directly into systemic circulation through jugular vein, avoid first pass metabolism and gastric or enzymatic degradation (Lamey et al., 1990; McElnay e al., 1990). The buccal dosage forms are easily applied and removed in case of any emergency condition because of its easy accessibility (De vries etal., 1991; Rathbone MJ et al., 1994; Senel S et al., 2001).In reported studies showed permeability of water across buccal mucosa is ten times higher than that of skin (Lesch C et al., 1989) In another study showed permeability constants of water and Horseradish peroxidise were more across buccal mucosa compared to surface skin (Squier CA et al., 1985).

Advantages and Disadvantages of Buccal drug delivery

The advantages for oral buccal delivery include:

1. More patient compliance and convenience.
2. Targeted delivery in treating oral cavity of local diseases.
3. Best for protein and peptide delivery.
4. Prominent for quick-dissolving dosage forms.
5. Dosage form administration can be done at anywhere without water.
6. Increases drug bioavailability.

The disadvantages in oral mucosal route are:

1. For drugs that are bitter and irritable need taste masking.
2. The area is small (100 to 170 cm^2) for drug absorption when compared to gastro intestinal absorption.
3. Saliva in mouth and tongue makes difficult for dosage form to stay in contact with mucosa.

Mechanisms involved in buccal drug delivery

The drug molecules or any substances are transported across oral epithelial cells by carrier mediated diffusion, passive diffusion, active transport and endocytosis.

Passive Diffusion

The un-ionized form of drug molecules transfer through oral mucosa is by passive diffusion mechanism (McElnay e al., 1990; Siegel IA et al., 1971). This passive diffusion process is first shown in buccal absorption studies with series of amphetamine. The optical isomers of amphetamine drug when given alone or with mixture of other drugs absorbed to the same extent and depended on concentration of un-ionized lipid soluble form (Schumann W et al., 1971; Shojaei AH et al., 1998). There are many other studies related to passive diffusion process across oral mucosa (Squier CA et al., 1999; Rathbone MJ et al., 1991). The physicochemical properties of membrane and drug give transport rate across biological membrane under passive diffusion model (Rathbone MJ et al., 1994).

Carrier-mediated Transport

The nutrients and sugars absorption in oral cavity is done by carrier transport mechanism (Manning AS et al., 1976). Specialized mechanism is observed for transporting D-glucose in cultured containing stratified oral mucosal cells of human (Kimura T et al., 2002). In few studies absorption of D-glucose took place in the tongue dorsal surface and those authors suggested specialized transport system existed at this site (KurosakiY et al., 1998). Some studies showed that various glucose transporters were found in buccal mucosal cells and tongue (Oyama Y et al., 1999). The mechanism of carrier mediated transport takes place across oral cavity for absorption of vitamins like nicotinamide, nicotinic acid and L-ascorbic acid and depends on sodium ions. The *in vivo* studies of absorption of thiamine results saturation at high concentrations gave another support for carrier-mediated processes. Rabbits and hamster oral mucosal cells were used to examine energy dependent carrier mediated monocarboxylic acid transport. Some studies showed absorption for cefadroxil which is amino carrier transport in oral cavity of humans because of saturation phenomena (Kurosaki Y et al., 1992).

Methods in assessing buccal mucosa Permeability

The wide ranges of models are used in the preclinical setting to assess permeability of buccal mucosa and most appropriately can be known by *in vivo* method. While *in vitro* and *in situ* studies are instrumental dependent studies to know preclinical compound screening, elucidating mechanism involved in transport and assessing potential of penetration enhancer's usage in buccal transport improvement.

In Vitro Methods

An *in vitro* permeability studies determines barrier nature of a particular biological tissue because the drugs diffusion is studied in an environment where variables such as osmolarity, temperature and pH are easily controlled. While using *in vitro* method for predicting absorption of compounds across the buccal mucosa of human, an appropriate animal model needs to be chosen on the basis of its similarity in structure & permeability to the human buccal mucosa. The *in vitro* studies on permeation are commonly conducted in diffusion cells by using buccal mucosa of an appropriate animal model. The advantage of this *in vitro* diffusion cells is that the drug concentration that has actually diffused across the tissue can be determined over time and kinetics can be assessed. There are various diffusion cells that are used in the preclinical screening of compound permeability including Franz- type diffusion cells and flow-through cells (Zhang H et al., 1996).

In vitro studies using animal buccal mucosal membranes

The humans oral buccal mucosa is limitedly available, so that freshly excised animal mucosa are used for permeation studies. The buccal mucosa of selected animal species should be similar to humans in permeability, biochemistry and morphology. Many researchers worked on oral mucosa of rats and hamsters (Aungst BJ et al., 1988) which have keratinized surface and not appropriate model similar to non-keratinized human buccal mucosa. Rabbits have non keratinized mucosa and used in many permeation studies (Dowty ME et al., 1992).Due to small area of non-keratinized mucosa present in oral cavity of rabbits, there is often limit in its use for permeation studies. Theoral buccal mucosa of dogs and monkeys also have non-keratinized part and used as a similar model for human oral buccal mucosa; but the epithelium of this mucosa is thin and highly permeable compared to humans. The physiologies, anatomy, nutritional and metabolic action of pigs are similar to human beings. Because of this reason pigs became most used animals in research on human disease. The buccal mucosa of pig is also non-keratinized and same as human buccal mucosa in structure, morphology, thickness and composition. In reported studies showed that the tritiated water permeation through porcine oral buccal mucosa is showing results to that of human oral buccal mucosa and some recent studies also showed that there is similar permeation of mannitol and testosterone through the porcine and the human buccal mucosa (Nielsen HM et al., 2000).

Franz-Type Diffusion cells

The Franz-type diffusion cells are used to assess *in vitro* penetration of drugs across skin and in *vitro permeation* across sbuccal mucosa(Ceschel GC, 2002). The buccal mucosa is placed in between two chambers, one is receptor chamber and other is donor chamber. The drug solution is kept in donor chamber

and buffer solution is kept in receptor chamber for assessment. The temperature of the receptor phase need to be maintained at 37±1 °C and stirred with magnetic stirrer to maintain homogeneous condition. The aliquots of 3 ml are to be withdrawn at fixed time intervals and to be replaced with fresh medium of equal volume withdrawn. The samples are to be analyzed using UV-Visible spectrophotometer and amount of drug released at different time intervals are calculated.

Flow-Through Diffusion cells

The flow through diffusion cells is also used for permeation studies to assess buccal mucosa similar tofranz diffusion cell. This flow across diffusion cell differs from franz diffusion cell with no closed donor chamber and buccal mucosa exposes to air and results in drying of tissue and causes death(Xiang J et al., 2002). In this diffusion cell the receptor solution flows down the placed buccal mucosa and there will be no drug accumulation in receptor chamber. The receptor solution is collected at frequent time intervals and analysed using UV spectrophotometer to know the permeated or diffused drug from buccalmucosa.

In Vivo Methods

Buccal absorption Test

The buccal absorption test is the most significant method to assess permeability of buccal mucosa. A drug solution of known amount was taken and swirled in subject oral cavity for some time period and expelled out into container. The subject is again rinsed with water or buffer solution and expelled into drug solution container. This combined drug solution and rinsed solution was analyzed for drug content. The difference between initially known drug solution and final drug concentration after completion of swirling and rinsing gives the drug quantity taken up by oral mucosa. To identify the salivary production throughout this test a correction factor was introduced by Dearden and Tomlinson, 1971. Some studies showed addition of marker compound like phenol red or polyethylene glycol to the swirling solution estimates salivary dilution and accidental swallowing of solution (Tucker IG et al., 1988). Tucker, 1988 modified the original test to determine the kinetic profile by taking swirled solution samples from oral cavity for every few minutes without removing the whole solution. By this modified studies the absorption kinetics of drug in oral cavity can be studied in each subject. This test is convenient to perform, do not require any blood samples and can assess both rate and extent of drug loss. The major disadvantage with this test is not determining blood samples and because of that the disappeared drug from swirling solution cannot be equated to amount of drug entering into the systemic solution. The absorption is done through all surfaces of oral cavity because the solution is swirled in entire oral cavity.

Perfusion cells

Perfusion cells are designed to clamp or attach at particular mucosa in oral cavity of humans and animals. In this technique the drug solution is perfused through perfusion cell and absorption of drug is achieved by disappeared drug from perforate. The leakage of drug solution and inter subject variability are the major drawbacks with perfusion cells. The information by collecting saliva and identifying its drug concentration would be helpful to know the drug plasma concentration (Yamahara H et al., 1990).

Buccal Dosage Forms

Solid buccal DosageForms

Buccal tablets

The buccal tablets are those solid dosage forms which are used in both systemic and local drug delivery. They releases drug either in single direction or multi direction which contains backing layer of impermeable nature (Jinsong H et al., 2003).

Bioadhesive microparticles and nanoparticles

Bioadhesive microparticles and nanoparticles are given either in suspension or paste or ointment or aerosols form. Bioadhesive polymers like polycarbophil, carbopol and chitosan are used in their pharmaceutical preparation (El Samaligy et al., 2006a).

Bioadhesive Wafers

The bioadhesive wafers are one of the buccal formulations mainly used in periodontal drug delivery. The surface layer of bioadhesive wafer possesses adhesive properties and backing layer have antimicrobial agents, biodegradable and matrix polymers.

Bioadhesive Lozenges

Lozenges contain medicaments with flavouring and sweetening agents used in mouth infection and local irritation. These lozenges are mostly used for cough.

Pastilles

Pastilles are the most recently developed slow dissolving intraoral dosage form for buccal administration. Pastilles are similar to lozenges but change in composition of added ingredients. Pastilles contain glycerol and gelatin, prepared by thick, syrupy solution of the desired ingredients and then pouring it into a mould which has been coated to resist sticking. Once dry the solution and hardens, the pastilles can be unmolded. Advantages of pastilles over tablets are flexibility, elastic, comfort, and soft. Cocaine pastilles were developed in 1800's and singers used for vocal huskiness, hoarseness. Penicillin agar pastilles were prepared with gelatin and agar by Greey and Macdonald, 1945.

Semi-Solid dosage forms

Medicated chewing gums

The formulation containing chewing gums are semi solid mucosal dosage forms used in replacement of nicotine. Caffeine chewing gum having brand name Stay Alert® was prepared for sleeping problem and Nicotine chewing gum (e.g., Nicorette® and Nicotinell®) for smoking cessation.

Adhesive gels

There are several gels available to deliver across mucosa and shows sustained action. Adhesive gel is prepared using polyacrylic acid helps to bind to mucosa for longer time and provide sustained action. Hydrogels are novel and advanced mucoadhesive formulations used for controlled release drug delivery.

Buccal patches/Films

The buccal patches have backing layer, bio adhesive surface and reservoir layer with drug to release in controlled manner. Solvent casting and hot melt extrusion methods are used to prepare buccal patches or films.

Liquid dosage forms

Liquid dosage forms like antibacterial mouthwashes and mouth-freshener are available in solutions and suspension forms. The viscous liquids are used in coating buccal surface as protectants to mucosal surface. The artificial saliva solutions are used in treating dry mouth and they are retained on mucosal surface for lubrication. Sodium carboxy methyl cellulose is used as a bio adhesive polymer in these artificial saliva solutions (Chinna reddy P etal, 2011).

Preparation of pastilles

The pastilles were prepared with modified method reported in British Pharmaceutical Codex, 1907. Accurately weighed 1.5 g of gelatin was transferred into 25 ml glass beaker. To gelatin 5 ml phosphate bufferpH7.4 was added and heated at 60 ºC on water bath to get complete dissolution. Accurately weighed 445 mg of carbopol and 1 g of sugar were added while stirring and heated until they dissolve in gelatin base. Glycerol of 1 g, sodium saccharin 5 mg was weighed and introduced to the above mixture. To this mixture liposomal dispersion containing 50 mg drug was added under stirring. Finally the mixture was transferred into 5 moulds of diameter 15 mm and cooled in freezer condition for solidification. The pastilles are stored in tightly closed container in refrigerator at 2-8 °C until further use.

Evaluation tests for pastilles -

Pastilles are evaluated for quality control parameters like mass thickness, folding endurance, uniformity, pH determination, *in vitro* swelling studies of buccoadhesive strength, *ex vivo* mucoadhesion time, permeation studies, *in vitro and in vivo* drug release.

Dimensions of pastilles

The diameter and thickness for prepared pastilles were determined by vernier caliper.

Fig 1.3: Appearance of pastilles

Average weight and weight variation

Twenty pastilles were taken and their weight was determined individually and collectively on a digital weighing balance. The weight variation was calculated using the following formula (Peck G et al., 1989).

$$Weight\ Variation = \frac{\text{Individual Weight} - \text{Average Weight}}{\text{Average Weight}} X100$$

Drug content estimation

Drug content estimation was done by dissolving one pastille in sufficient quantity of phosphate buffer pH 7.4 and diluted up to 100 ml in volumetric flask. The sample was filtered and diluted suitable. The absorbance of the resulting solution was measured using UV-Visible spectrophotometer at 475 nm against phosphate buffer pH 7.4. From the observed absorbance drug content in pastilles was calculated.

Swelling and Erosion studies

Swelling and erosion studies for pastilles were determined gravimetrically in phosphate buffer of pH 6.8 which was attached to pre-weighed glass *petri* dish and supported using adhesive sealant. Three pastilles were weighed individually (W_1) and immersed separately in phosphate buffer of pH 6.8. The pastille was removed after 1 h from *petri* dish and excess water present on surface was removed using blotting paper. After that the swollen pastilles were then reweighed (W_2) and swelling index (SI), erosion were calculated using formula given in below equation.

$$SwellingIndex = \frac{W_1 - W_2}{W_2} X100$$

$$Erosion = \frac{W_1 - W_2}{W_2} X100$$

Where, W_1 = pastille initial weight

W_2 = pastille final weight

Moisture absorption study

The moisture absorption study indicates the relative moisture uptake of the polymers employed in the formulation of pastilles and also the integrity of pastilles after absorption of moisture. Moisture absorption studies have been performed using 5% w/v agar in distilled water, which while hot was transferred to petri plates and allowed to solidify (Khurana R et al., 2000). Then pastille was weighed and placed in desiccators overnight prior to the study to remove moisture and placed on the surface of agar plate for 2 h. The pastilles were weighed again and percentage of absorbed moisture was calculated using the formula.

$$\%\ MoistureAbsorbed = \frac{W_1 - W_2}{W_2} X100$$

Where, W_1 = initial weight of the pastille

W_2 = final weight of the pastille

Study of pH

One pastille was taken and dissolved in 100ml of 37 °C distilled water. The pH was measured by using pH meter and allowed it to equilibrate for one minute (Bottenberg P et al., 1991).

Bio adhesionTime

The mucoadhesion time was studied after application of the pastille on freshly cut porcine buccal mucosa. The fresh porcine buccal mucosa was attached on the glass slide. One side of the pastille was wetted with 1 drop of phosphate buffer pH 6.8 and placed on the porcine buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 ml of the phosphate buffer pH 6.8 under magnetic stirrer at 300 rpm to maintain homogeneous condition. The time was recorded as mucoadhesion time to detach the pastille from porcine buccal mucosa (Vishnu MP et al., 2007).

Bioadhesive strength

Bioadhesive strength of the pastille was measured on the "modified physical balance method" using porcine buccal membrane as the model mucosal membrane. The fresh porcine buccal mucosa was cut and washed with phosphate buffer pH 6.8. A piece of mucosa was tied to the glass slide that was moistened with phosphate buffer pH 6.8. The pastille was stuck to the lower side of another glass slide with glue. The both pans were balanced by adding an appropriate weight on the left hand pan. The glass slide with mucosa was placed with appropriate support, so that the pastille touches the mucosa. Weights were added slowly on the right hand pan until the pastille detach from the mucosal surface. The weight required to detach the pastille from the mucosal surface gave the bioadhesive strength. The experiment was performed in triplicate and average value was calculated (Ramana V et al., 2007).

***In vitro* Drug Release Studies**

The *in vitro* drug dissolution studies were performed by using USP dissolution test apparatus II (paddle method). The dissolution test was conducted in 500 ml of phosphate buffer pH 7.4 as dissolution media (USP 2007). The speed of the paddle was 75 rpm. The temperature was main 37±0.5 ºC. One pastille was added in a dissolution medium. The aliquots of 5 ml were withdrawn at the time interval of 10, 20, 30, 45 and 60 minutes and replaced with equal volume of fresh dissolution medium. The samples were suitable diluted and analyzed for amount of drug at 475 nm in a UV-visible spectrophotometer. The percentage drug release at various time intervals was calculated. The study was conducted in triplicate.

Recent Developments in Pastilles

Global pharmaceutical companies are also continuously working on suitable buccal drug delivery system but very few formulations are available in market and under clinical trials. The lipophilic hydrogels, buccal sprays and buccal liposomal vesicles are reported by researchers in studies to deliver peptides and vitamins. Some authors also reported glycerylmonooleate in lamellar crystalline phases is a buccal carrier in peptide delivery (Lee J et al., 2000). A novel insulin buccal aerosol was developed recently and commercially available in market with brand name Oralin by Generex Biotechnology (Modi G et al., 2002). Reported methods with phospholipid vesicles and transfersomes are available for insulin through buccal delivery (Yang TJ et al., 2002).Some commercial pastilles available in table 1.4

Table 1.4: Marketed formulations of pastilles

S.no.	API	Dosage form	Brand name	Manufacturer
1	Curcumin	Pastilles	Curkey	Inzpera Healthsciences Limited
2	Nystatin	Pastilles	Mycostatin	Bristol myerssquibb manufacturing company
3	Nicotine	Pastilles	Niclonz	Intas Pharmaceuticals Limited
4	Nicotine	Pastilles	Habbicure	HET Enterprises
5	Nicotine	Pastilles	Frenquit	Alkem Laboratories Limited
6	Menthol	Pastilles	Olbas	G.R Lane Health Products
7	Alpha glycerylphosphorylcholine	Pastilles	Alpha Gpc	Intas Pharmaceuticals Limited
8	Alpha glycerylphosphorylcholine	Pastilles	Megacholin	Aristo Pharmaceutical Private Limited

Conclusion

It was concluded that pastilles have numerous advantages above the conventional drug delivery system. The mucosa is highly vascularised and lymphatic drainage and avoiding first-pass metabolism. Buccal drug delivery is vast area for continued research with the aim of systematic delivery of orally inefficient drugs. So, in the upcoming years, it is predictable that pastilles are one of the vital dosage forms in pharmaceutical system.

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