FORMULATIONANDEVALUATIONOFVORICONAZOLE BUCCAL PATCHES BY USING SELECTED POLYMERS

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Abstract:

The aim of the present study is to formulate and evaluate Voriconazole Buccal Patches. Voriconazole is a triazole antifungal drug that is generally used to treat serious, invasive fungal infections. These are generally seen in patients who are immune compromised, and include invasive candidiasis, invasive aspergillosis, and certain emerging fungal infections. In the present study buccal drug delivery of Voriconazole was developed Matrix type of buccal patches was developed by using polymers such as Chitosan and Eudragit S 100. Buccal patches were prepared by employing solvent casting method. Propylene glycol and Tween80 were selected as both permeation enhancer and plasticizer. Drug excipient compatibility studies were carried out by using FTIR, and it was observed that there were no interactions between drug and polymers. Formulations were prepared by the varying concentrations polymers ranging from F1-F6, and all the formulations were evaluated for various physical parameters such as Physical appearance, Flatness, Weight variation, Thickness, Folding endurance, Drug content, Moisture uptake, Moisture content. All the results were found to be were found to be within the pharmacoepial limits, invitro drug release studies done by using dialysis membrane. Among all the 06 formulations F4 formulation which contain Eudragit S 100 100mg has shown 95.76% cumulative drug release within 12 hours. For F4 formulation release kinetics were plotted and the Regression coefficient value was found to be high for Korsemeyer Peppas model plot i.e., 0.999.

Key words: *Voriconazole, Buccal Patches, Chitosan and Eudragit S 100*

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INTRODUCTION:

Buccal drug delivery is one of the novel drug delivery systems. It localized the delivery of drug to tissues of the oral cavity for the treatment of bacterial and fungal infection as well as periodontal disease. Buccal drug delivery also a safer mode of drug delivery system and can be able to remove in case of toxicity and adverse effect. Buccal mucosa has an excellent accessibility, which leads to direct access to systemic circulation through the internal jugular vein bypasses the drugs from hepatic first pass metabolism [1]. The administration of drug through buccal route provides a direct entry of drug molecule into the systemic circulation via avoiding the first pass metabolism. It is possible bypass of first pass effect and avoidance of pre-systemic elimination within the gastrointestinal tract. Buccal route is preferred the drugs having poor bioavailability because of high first pass metabolism. Mucoadhesion is the phenomenon between two materials which are held together for prolong period of time by interfacial force. It is generally referred as mucoadhesion when interaction occurs between polymer and epithelial surface. Buccal patches are highly flexible and thus much more readily tolerated by the patient than tablets. Some of the potential sites for attachment of any mucoadhesive system include buccal cavity, nasal cavity, eyes, vagina, rectal area, sublingual route and gastrointestinal area. Moreover, the buccal films are able to protect the wound surface, thus reducing pain and treating oral diseases more effectively [2].

ORAL MUCOSA

The total area of the oral cavity is $100cms^2$. One third is the buccal surface, which is lined with an epithelium of about 0.5mm thickness. The main role of oral mucosa is protection of tissue underlying. Lipid based permeability barriers in epithelium layer protect the tissues from fluid loss and also from the attack of harmful environmental agents like microbial toxins, antigens, carcinogens, enzymes etc. Oral epithelium proliferation time is 5-6 days. Oral cavity is that area of mouth delineated by the lips, cheeks, hard palate, soft palate and floor of mouth. The oral cavity consists of two regions. Outer oral vestibule which is bounded by cheeks, lips, teeth and gingival (gums). Oral cavity proper which extends from teeth and gums back to the faucets (which lead to pharynx) with the roof comprising the hard and soft palate. The tongue projects from the floor of the cavity [3].

FUNCTIONS OF ORAL CAVITY

➢ It helps in chewing, mastication and mixing of food stuff.
➢ It is Helps to lubricate the food material and bolus.
➢ To identify the ingested material by taste buds of tongue.
➢ To initiate the carbohydrate and fat metabolism.
➢ As a portal for intake of food material and water.
➢ To aid in speech and breathing process [4]

Methods to increase drug delivery via buccal route

1.Permeation enhancers: The epithelium that lines the buccal mucosa is a very effective barrier to the absorption of drugs. Sub-stances that facilitate the permeation through buccal mucosa are referred as absorption enhancers. As most of the absorption enhancers were originally designed for increase the absorption of drug and improved efficacy and reduced toxicity. However, the selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other excipients. In some cases usage of enhancers in combination has shown synergistic effect than the individual enhancers [5]. The efficacy of enhancer in one site is not same in the other site because of differences in cellular morphology, membrane thickness, enzymatic activity, lipid composition and potential protein interactions are structural and functional properties[5]. The most common absorption enhancers are azone, fatty acids, bile salts and surfactants such as sodium dodecyl sulfate. Solutions/gels of Chitosan were also found to promote the transport of mannitol and fluorescent-labeled dextrans across a tissue culture model of the buccal epithelium while Glyceryl monooleates were reported to enhance peptide absorption by a co-transport mechanism [6].

MECHANISM

Mechanisms by which penetration enhancers are thought to improve mucosal absorption are as follows.

Changing mucus rheology: Mucus forms viscoelastic layer of varying thickness that affects drug absorption. Further, saliva covering the mucus layers also hinders the absorption. Some permeation enhancers act by reducing the viscosity of the mucus and saliva overcomes this barrier.

Increasing the fluidity of lipid bilayer membrane: The most accepted mechanism of drug absorption through buccal mucosa is intracellular route. Some enhancers disturb the intracellular lipid packing by interaction with either lipid packing by interaction with either

lipid or protein components.

Acting on the components at tight junctions: Some enhancers act on desmosomes, a major component at the tight junctions there by increases drug absorption.

By overcoming the enzymatic barrier: These act by inhibiting the various peptidases and proteases present within buccal mucosa, thereby overcoming the enzymatic barrier. In addition, changes in membrane fluidity also alter the enzymatic activity indirectly.

Increasing the thermodynamic activity of drugs: Some enhancers increase the solubility of drug there by alters the partition coefficient. This leads to in-creased thermodynamic activity resulting better absorption. Surfactants such as anionic, cationic, nonionic and bile salts increases permeability of drugs by perturbation of intercellular lipids whereas chelators act by interfering with the calcium ions, fatty acids by increasing fluidity of phospholipids and positively charged polymers by ionic interaction with negative charge on the mucosal surface [7].

Prodrug: Nalbuphine and naloxone bitter drugs when administered to dogs via buccal mucosa causes excess salivation and swallowing. As a result, the drug exhibited low bioavailability. Administration of nalbuphine and naloxone in Prodrug form caused no adverse effects, with bioavailability ranging from 35 to 50% showing marked improvement over the oral bioavailability of these compounds.

pH: The *in vitro* permeability of acyclovir was found to be pH dependent with an increase in flux and permeability coefficient at both pH extremes (pH 3.3 and 8.8), as compared to the mid-range values (pH 4.1, 5.8, and 7.0).

NOVEL BUCCAL DOSAGE FORMS

The novel type buccal dosage forms include buccal adhesive patches, tablets, films, semisolids (ointments and gels) and powders.

Patches and Films [8]

Patches consists of two laminates, with an aqueous solution of the adhesive polymer being cast onto an impermeable backing sheet, which is then cut into the required oval shape . A novel mucosal adhesive film called "Zilactin" - consisting of an alcoholic solution of hydroxyl propyl cellulose and three organic acids. The film which is applied to the oral mucosal can be retained in place for at least 12 hours even when it is challenged with fluids. E.g. buccal film of salbutamol.

Buccal mucoadhesive tablets

Mucoadhesive tablets are dry dosage forms and

it is to be moistened prior to placing in contact with buccal mucosa . It is double layer tablet, consisting of adhesive matrix layer of polyacrylic acid and hydroxy propyl cellulose with an inner core of cocoa butter containing insulin and a penetration enhancer (sodium glycocholate).

Semisolid Preparations (Ointments and Gels)

One of the original oral mucoadhesive delivery systems – "orabase"– consists of finely ground pectin, gelatin and sodium carboxy methyl cellulose dispersed in a poly (ethylene) and a mineral oil gel base, which can be maintained at its site of application for 15-150 minutes. Example: Chitosan glutamate buccal hydrogel with local anesthetics activity .

Powders

Beclomethasone and Hydroxy propyl cellulose in powder form when sprayed onto the oral mucosa of rats, a significant increase in the residence time relative to an oral solution is seen, and 2.5% of beclomethasone is retained on buccal mucosa for over 4 hours

Buccal sprays

Generex bio technologies have been introduced insulin spray . This technology is being used to develop a formulation for buccal delivery of insulin for the treatment of type -1 diabetes buccal spray delivers a mist of fine droplets onto mucosal membrane probably on to mucin layer. e.g. Estradiol sprays [9,10].

Advantages of Buccal Patches

The oral mucosa has a rich blood supply. Drugs are absorbed from the oral cavity through the oral mucosa, and transported through the deep lingual or facial vein, internal jugular vein and braciocephalic vein into the systemic circulation. Buccal administration, the drug gains direct entry into the systemic circulation thereby bypassing thefirstpass effect. Contact wit h the digestivefluids of gastrointestinal tract

is avoided which might be unsuitable for stability of many drugs like insulin or other proteins, peptides and steroids. In addition, the rate of drug absorption is not influenced by food or gastric emptying rate [11].

The area of buccal membrane is sufficiently large to allow a delivery system to be placed at different occasions, additionally; there are two areas of buccal membranes per mouth, which would allow buccal drug delivery systems to be placed, alternatively on the left and right buccal membranes.

Buccal patch has been well known for its good accessibility to the membranes that line the oral

cavity, which makes application the oral cavity, which makes application painless and with comfort.

Patients can control the period of administration or terminate delivery in case of emergencies. The buccal drug delivery systems easily administered into the buccal cavity. The novel buccal dosage forms exhibits better patient compliance.

Disadvantages of Buccal Drug Delivery System

Low permeability of the buccal membrane, specifically when compared to the sublingual membrane.

Smaller surface area. The total surface area of membranes of the oral cavity available for drug absorption is 170 cm2 of which ~50 cm represents non-keratinized tissues, including the buccal membrane.

The continuous secretion of saliva (0.5-2 l/day) leads to subsequent dilution of the drug.

Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and, ultimately, the involuntary removal of the dosage form

These are some of the problems that are associated with current buccal drug delivery system [12,13].

General considerations in designing dosage forms
Physiological aspects

Due to the constant flow of saliva and regular movement of tissues present in the oral cavity the local delivery of the drugs in oral cavity is the most challenging aspect. Due to this, the residence time of the drugs for this route is very short. The buccal mucoadhesive formulations are being used to overcome this problem. The bioadhesive polymers are been use for improving the residence time in the buccal mucosa, and hence increase the absorption of drugs delivered by this route. Due to the local absorption of drugs, side effects are also being reduced as compared to in case of systemic delivery. Generally, a buccal delivery device should have the size of about 1-3 cm^2 and the daily drug dose should be not more than 25 mg. An ellipsoid or circular shapes are being the most acceptable shapes for buccal delivery device.

Pathological aspects

The barrier property of buccal mucosa is mainly due to the presence of epithelial tissue. The thickness of epithelial tissue can be affected by many diseases that may change the barrier property of epithelial tissue. Some diseases or treatments may cause the alteration in rate of mucus secretion. These changes at the mucosal surface due to various pathological

conditions may affect the residence time buccal delivery device.

Pharmacological aspects

The design and formulation of a buccal delivery dosage form depends upon the nature of delivery (local or systemic), drug targeting site and mucosal site to be treated. The buccal delivery is generally preferred for systemic delivery as compared to the local delivery of drugs.

Pharmaceutical aspects

The buccal drug delivery system is generally used for desired absorption of poorly water soluble drugs. For this purpose, firstly the water solubility of the drug is enhanced by using specific solubility enhancement method e.g., by forming complex with cyclodextrin. Hence by improving solubility, the absorption of drug also get increased in buccal mucosa. Here are many other factors that effect the release and penetration of drug, must be optimized during formulation design. In addition to this required physicochemical characteristics required for desired release of and absorption of drug, organoleptic properties of the drug as well as buccal dosage form should also be considered during its formulation design. Some excipients such as plasticizers and penetration enhancers can be used in the formulations to enhance their effectiveness and acceptability. As the buccal mucosa is less permeable, so in order to enhance the permeability, various penetration enhancers can be used. Some commonly used penetration enhancers are bile salts, fatty acids, and sodium lauryl sulphate. Some enzyme inhibitors may be used to inhibiting the degradation of drug by various enzymes present in the saliva due to which the bioavailability of drug can be improved. Here are some polymers such as carbopol, polycarbophil that can inhibit certain proteolytic enzymes (trypsin, carbo-peptidases etc.,)[14]. pH of delivery device is another pharmaceutical factor that should be considered during formulation of buccal delivery devices containing ionisable drugs. The pH of buccal device should be near to neutral as the pH of saliva is from 6.6 to 7.4. The large differences in pH may cause irritation on the mucosal site. On the basis of their geometry, the buccal mucoadhesive dosage forms can be categorized into three types as given below [15].

Type I: In this there is a single layer containing dosage form which provides multidirectional drug release. The main disadvantage of this type is that the drug loss is high by swallowing.

Type II: It contains the drug loaded bioadhesive layer covered by impermeable backing membrane. The backing membrane covers only the opposite side from the site of attachment hence preventing the drug

loss from the upper surface of device.

Type III: In this type, all sides of drug loaded mucoadhesive layer are covered by impermeable except the side that attaches the target area. It is a unidirectional drug flow preventing all kinds of unwanted drug loss.
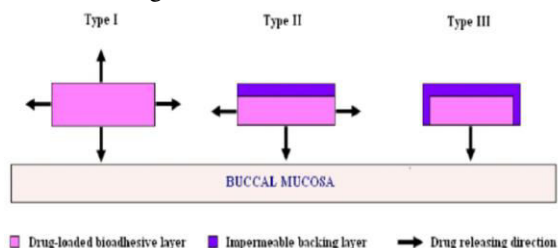

FIGURE 1 TYPES OF BUCCAL MUCOADHESIVE DOSAGE FORM MECHANISM OF BUCCAL ABSORPTION

Buccal drug absorption occurs by passive diffusion of the nonionized species, a process governed primarily by a concentration gradient, through the intercellular spaces of the epithelium. The passive transport of non-ionic species across the lipid membrane of the buccal cavity is the primary transport mechanism. The buccal mucosa has been said to be a lipoidal barrier to the passage of drugs, as is the case with many other mucosal membrane and the more lipophilic the drug molecule, the more readily it is absorbed [16]. The dynamics of buccal absorption of drugs could be adequately described by first order rate process. Several potential barriers to buccal drug absorption have been identified. Dearden and Tomlison (1971) pointed out that salivary secretion alters the buccal absorption kinetics from drug solution by changing the concentration of drug in the mouth. The linear relationship between salivary secretion and time is given as follows. Where,

M-Mass of drug in mouth at time t, K-Proportionality constant, C-Concentration of drug in mouth at time, Vi - The volume of solution put into mouth cavity and Vt - Salivary secretion rate.

BIOADHESION AND MUCOADHESION[17]

The term bioadhesion refers to any bond formed between two biological surfaces or a bond between a biological and a synthetic surface. In the case of bioadhesive drug delivery systems, it is a bond formed between polymers and soft tissues. If the bond is formed between mucus and polymer, it is described as mucoadhesion. Although the target of many bioadhesive delivery systems may be a soft tissue cell layer (i.e. epithelial cells), the actual adhesive bond may form with either the cell layer, a mucous layer or a combination of the two. In instances in which bonds form between mucus and polymer, the term mucoadhesion is used synonymously with bioadhesion. In general, bioadhesion is an all-inclusive term used to describe adhesive interactions with any biological or biologically derived substance, and mucoadhesion is used only when describing a bond involving mucus or a mucosal surface.

MECHANISM OF BIOADHESION

The mechanisms responsible for the formation of bioadhesive bonds are not completely clear. Most research has been focused on analyzing bioadhesive interactions between polymer hydrogels and soft tissues [18].

Mechanism of bioadhesion can be described in three successive steps

1. Wetting and swelling of polymer to permit intimate contact with biological tissue.
2. Interpenetration of bioadhesive polymer chains and entanglement of polymer and mucin chains.
3. Formation of weak chemical bonds between entangled chains.

> ➢ Following are the some of polymer characteristics that are required to obtain adhesion , Sufficient quantities of hydrogen-bonding chemical groups (-OH and COOH).
> ➢ Anionic surface charges.
> ➢ High molecular weight of mucin strands with flexible polymer chains and/or interpenetration of mucin strands into a porous polymer substrate.

Theories of Bioadhesion: High chain flexibility and Surface tension that will induce spreading into the mucus layer. Each of these characteristics favors the formation of bonds that are either chemical or mechanical in origin Chemical bonds include strong primary bonds (i.e. covalent bonds), as well as weaker secondary forces such as ionic bonds, vander-Waals interactions and hydrogen bonds. Both types of interactions have been exploited in developing bioadhesive drug delivery systems[19].

Mechanical bonds can be thought of as physical connections between surfaces, similar to interlocking puzzle pieces. Macroscopically, they involve the inclusion of one substance in the cracks or crevices of another. On a microscopic scale, they can involve physical entanglement Following are the theories that have been adopted to study bio adhesion.

i) The Electronic Theory: According to this theory, electron transfer occurs upon contact of an adhesive polymer with a mucus glycoprotein network because of differences in their electronic structures. This results in the formation of an electrical double layer at the interface. Adhesion occurs due to attractive forces across the double layer[20].

ii) The Adsorption Theory: According to this theory, after an initial contact between two surfaces,

the material adheres because of surface forces acting between the atoms in the two surfaces. Two types of chemical bonds resulting from these forces are:

> ➤ Primary chemical bonds of covalent nature.
> ➤ Secondary chemical bonds having many different forces of attraction including electrostatic forces, Vander Waals forces, and hydrogen and hydrophobic bonds [21].

iii) The Wetting Theory: This theory describes the ability of mucus to spread and develop intimate contact with its corresponding substrate which is one important factor in bond formation. The wetting theory uses interfacial tensions to predict spreading and in turn adhesion.

iv) Diffusion Theory: According to this theory the polymer chains and the mucus mix to a sufficient depth to create a semi permanent adhesive bond. The exact depth to which the polymer chains penetrate the mucus. The depends on the diffusion coefficient and the time of contact. This diffusion coefficient, in turn depends on the value of molecular weight between cross-links and decreases significantly as the linking density increases.

v) The Fracture Theory: This theory analyzes the forces required to separate two surfaces after adhesion. The maximum tensile stress produced during detachment can be determined by dividing the maximum force of detachment by the total surface area involved in the adhesive interaction. It does not require measuring entanglement, diffusion or interpenetration of polymer chains.

Factors affecting Buccal Absorption: The oral cavity is a complex environment for drug delivery as there are many interdependent and independent factors which reduce the absorbable concentration at the site of absorption.

> ➤ **Membrane Factors:** This involves degree of keratinization, surface area available for absorption, mucus layer of salivarypellicle, intercellular lipids of epithelium, basement membrane and lamina propria. In addition, the absorptive membrane thickness, blood supply/ lymph drainage, cell renewal and enzyme content will all contribute to reducing the rate and amount of drug entering the systemic circulation.
> ➤ **Environmental Factors**

Saliva: The thin film of saliva coats throughout the lining of buccal mucosa and is called salivary pellicle or film. The thickness of salivary film is 0.07 to 0.10 mm. The thickness, composition and movement of this film affect the rate of buccal absorption.

Salivary glands: The minor salivary glands are located in epithelial or deep epithelial region of buccal mucosa. They constantly secrete mucus on surface of buccal mucosa. Although, mucus helps to retain mucoadhesive dosage forms, it is potential barrier to drug penetration.

Movement of buccal tissues: Buccal region of oral cavity shows less active movements. The mucoadhesive polymers are to be incorporated to keep dosage form at buccal region for long periods to withstand tissue movements during talking and if possible during eating food or swallowing.

Composition of Buccal Patches

Voriconazole: Voriconazole (Vfend®) was approved by the Food and Drug Administration (FDA) for the treatment of deadly fungal infections. Voriconazole is classified as a triazole antifungal agent. Other agents in this class are fluconazole (Diflucan®) and itraconazole (Sporonox®). This medication is indicated for the primary treatment of acute invasive aspergillosis. Additional agents include intravenous amphotericin and oral and/or intravenous itraconazole therapies. It has also been approved as salvage therapy for rare but serious fungal infections caused by Scedosporium apiospermum and Fusarium spp. Unlike other agents, Voriconazole has been approved in both oral and intravenous (IV) formulations. Voriconazole (Vfend®) is indicated for use in the treatment of the following fungal infections[22,23]:

> ➤ Treatment of invasive aspergillosis. Treatments of invasive aspergillosis in clinical trials, the majority of isolates recovered were Asperillus fumigatus. There was a small number of cases of culture-proven disease due to species of Aspergillus other than a fumigatus.
> ➤ Treatment of serious fungal infections caused by Scedosporium apiospermum and Fusarium including Fusarium solani, in patients intolerant of, or refractory to, other therapy.

Voriconazole (Vfend®) is a triazole antifungal agent. The primary mode of action or Voriconazole is the inhibition of fungal cytochrome P-450-medicted 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosyntheses. The accumulation of 14 alpha-methyl sterols correlated with the subsequent loss of ergosterol in the fungal cell wall and may be responsible for the antifungal activity of Voriconazole. Voriconazole has been shown to be more selective for fungal fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

> ➤ **Polymers (adhesive layer):** Hydroxyethylc ellulose, hydroxyl

propyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, carbopol and other mucoadhesive polymers.

- **Diluents:** Lactose DC is selected as diluent for its high aqueous solubility, its flavouring characteristics, and its physico-mechanical properties, which make it suitable for direct compression. Other example: microcrystalline starch and starch.
- **Sweetening agents:** Sucralose, aspartame, mannitol, etc.
- **Flavouring agents:** Menthol, vanillin, clove oil, etc.
- **Backing layer:** Ethyl cellulose, Poly vinyl alcohol etc.
- **Penetration enhancer:** Cyano acrylate, etc.
- **Plasticizers:** PEG-100, 400, propylene glycol, etc.

Method of Preparation: Two methods are used to prepare adhesive patches.

1.   Solvent casting [24,25]

In this method, all patch excipients including the drug co-dispersed in an organic solvent and coated onto a sheet of release liner. After solvent evaporation a thin layer of the protective backing material is laminated onto the sheet of coated release liner to form a laminate that is die-cut to form patches of the desired size and geometry.

Flow chart of Solvent casting Method Water soluble ingredient is dissolve in water (H2O) and API and other agent are dissolving in suitable solvent so as to form a clear solution.

Followed by both the solution are mixed
↓
Resulting solution in cast as a film is and allowed to dry
↓
Film is coated

2. Direct milling

Drug and excipients are mixed by kneading, usually without the presence of any liquids. After the mixing process, material is rolled on a release liner until the desired thickness is achieved. The backing material is then laminated as previously described . While there are only minor or even no differences in patch performance between patches fabricated by the two processes, the solvent-free process is preferred because there is no possibility of residual solvents and no associated solvent-related health issues .

Flow chart of Solvent casting Method

API and excipient are blended by direct milling
↓
Blended mixture is rolled with the help of roller

↓
Followed material is laminated
↓
Finally film is collected

A buccal adhesive system offers countless advantages in terms of economy, accessibility, administration, withdrawal and patient compliance. Research scientists are now looking out the traditional polymers for novel drug transport systems. From the recent years, pharmaceutical experts are finding various methods to develop buccal adhesive dosage forms and to improve the bioavailability of less orally bioavailable drugs. It is found that the second generation mucoadhesive polymer having great potential [26].

Mucoadhesive buccal patches have gained importance in drug delivery. The use of Natural polymers is increasing in the formulation of buccal patches. The mucosa is well supplied with both vascular and lymphatic drainage and first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract is avoided. The area is well suited for a retentive device and appears to be acceptable to the patient. This review focuses on the preparation of novel drug delivery systems which will provide least adverse effects and maximal therapeutic response [27].

MATERIALS

Voriconazole is a gift sample from NATCO LABS Hyderabad, Telangana, India. Chitosan, Methanol, PEG 400, Tween 80 from SD Fine Chemical Mumbai, India, Eudragit S 100 Dichloromethane from Merck Specialities Pvt Ltd India. Other ingredients were of analytical grade and purchased from local markets.

METHODS

I. Determination OF UV Absorption maxima:[28]

Voriconazole solution was prepared in 6.8 pH phosphate buffer and diluted suitably. The UV spectrum of the solution was taken on Lab India 3200 UV/Vis double beam Spectrophotometer. The Solution exhibited UV maxima at 274 nm. The procedure was repeated with pH 6.8 phosphate buffer

II. Preparation of Standard Calibration Curve of Voriconazole: 100 mg of Voriconazole was accurately weighed and dissolved in little amount of Methanol and make up the final volume up to 100 ml with pH 6.8 phosphate buffer to prepare stock solution. The 10 ml of stock solution was further

diluted with pH 6.8 phosphate buffer in 100ml to get 100µg/ml (working standard). Then 0.5,1,1.5,2and 2.5 ml of working standard was taken in 10 ml standard volumetric flask and made up the volume with pH 6.8 phosphate buffer. Then the absorbance was measured in a UV spectrophotometer at 274 nm against pH 6.8 phosphate buffer as blank.

III. Drug excipients interaction studies

FT-IR spectrum interpretation : IR spectral analysis was carried out using FT-IR by the KBr disc method. The sample and KBr were triturated and compressed to get the discs. The samples of pure drug, dummy formulation and optimized formulation were analyzed between wave numbers 4000.0 and 400.0 cm^{-1}.

IV. Selection of drug and other ingredients

- Voriconazole was selected as model drug based on its physico-chemical and biological properties and also based on its suitability for buccal drug delivery system.

- Chitosan (mg), Eudragit S100 (mg), Carbopol 940 (mg) were selected as matrix forming polymers.

- Propylene glycol and Tween80 were selected as permeation enhancer and plasticizer.

V. Formulation of buccal patches

Development of Buccal patches: Buccal drug delivery patches were prepared by solvent casting method.

Solvent casting method: CHITOSAN and EUDRAJIT S 100 were weighed in requisite ratios and they were then dissolved in dichloromethane and ethanol as solvent using magnetic stirrer. Voriconazole (300mg), Propylene glycol and Tween 80 was added to the above dispersion under continuous stirring. The uniform dispersion was poured in the Petri plate. The rate of evaporation of solvent was controlled by inverting cut funnel over the patches..

TABLE 1. FORMULATIONS OF VORICONAZOLE BUCCAL PATCH

INGREDIENTS	F1	F2	F3	F4	F5	F6
DRUG	300mg	300mg	300mg	300 mg	300 mg	300 mg
CHITOSAN	100 mg	200 mg	300 mg	-	-	-
EUDRAJIT S 100	-	-	-	100 mg	200 mg	300 mg
DICHLOROMETHANE	10ml	10ml	10ml	10ml	10ml	10ml
METHANOL	13.2ml	13.2ml	13.2ml	13.2ml	13.2ml	13.2ml
PEG 400	1ml	1ml	1ml	1ml	1ml	1ml
TWEEN 80	1ml	1ml	1ml	1ml	1ml	1ml

Evaluation of Buccal patch by physical methods [29,30]

Physical appearance: All the Buccal patches were visually inspected for color, clarity, flexibility & smoothness.

Thickness: This thickness of the patches was assessed at 3 different points using screw gauze. For each formulation, three randomly selected patches were used.

Weight variation: The three disks of 2x2 cm^2 was cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch- to- batch variation.

Flatness: Longitudinal strips were cut out from each patch, one the centre and two from either side. The length of each strip was measured and the variation in the length because of uniformity in flatness was measured by determining present constriction, considering 0% constriction equivalent to 100% flatness.

Folding endurance: The folding endurance was measured manually for the preparation patch. A strip of the films (4x3 cm) was cut evenly and repeatedly folded at the same place till it is broken.

Moisture uptake: The percent moisture absorption test was carried out to check the physical stability and integrity of the patch at high humid conditions. In the present study the moisture absorption capacities of the patch were determined in the following manner. The patches were placed in the desiccators containing 200 ml saturated solution of potassium chloride, to get the humidity inside the desiccators at 84 % RH. After 3 days the films were taken and weighed the percentage moisture absorption of the patch was found.

Percentage moisture absorbed = $\dfrac{Finalweight - Initialweight}{Initialweight} \times 100$

Moisture content: The patches were weighed individually and kept in a desiccators containing fused calcium chloride at 40 ºC for 24 h. The patches were reweighed until a constant weight was obtained.

Moisture content was calculated in percentage based on the difference between the initial and the constant final weights of the patches.

Swelling study: Completely dried membranes with a specified area (3.83 cm^2) were weighed and put in desiccators for 24 h. They were removed and exposed to relative humidity conditions of 75% (containing saturated solution of sodium chloride) in desiccators. Weight was taken on a single pan balance periodically until a constant weight was obtained. The swelling capacity of the membranes (in weight %) was calculated in terms of percentage increase in weight of membrane over the initial weight of the specimen. The experiments were carried out in triplicate and the average values were used for the calculation. The percentage degree of swelling (DS) was calculated as

DS (%) = Ws-Wd/Wd× 100

Where, W_s and W_d indicate the weight of the swollen and dry membranes respectively [31].

Drug content determination: The patch of area 3.83 cm^2 was cut and dissolved in PBS pH 7.4. Then solvent ethanol and dichloromethane, to make polymer soluble, were added to the mixture and the remaining volume was made up with PBS pH 7.4 to 100 ml in 100 ml volumetric flask. Then 1 ml was withdrawn from the solution and diluted to 10 ml. The absorbance of the solution was taken at 274 nm and concentration was calculated. By correcting dilution factor, the drug content was calculated.

Surface pH: For the determination of surface pH patch from each formulation was allowed to swell for 2 hrs in a Petridish containing 5 ml of phosphate buffer pH 6.8. The surface pH was measured by pH paper placed on the surface of patches and allowed to equilibrate for 1 min.

Evaluation of Buccal patch by permeation studies [32,33]

Diffusion cell: Permeation studies were carried out on Franz diffusion cells. The Franz diffusion cell contains two compartments, the donor and receptor compartment. The receptor compartment is 5mm and holds a volume of 15 ml. The receptor compartment is attached to a collecting tube which allows easy collection of hourly sample while the process of diffusion. The donor and the receptor compartment are held together with help of a clap and the diffusion cell was placed on the magnetic stirrer while diffusion studies carried.

The total area of the receptor compartment that is exposed to the Buccal patch for diffusion is 3.83 cm^2.

***Invitro* permeation studies using dialysis membrane:** *Invitro* permeation of Voriconazole from Buccal patches through dialysis membrane (Hi-Media) with molecular weight cut off of 12000 was studied. The membrane was mounted over a Franz diffusion cell and a buccal patch. The receiver compartment of the diffusion cell was filled with 15.0 ml of PBS pH 7.4 and the setup was placed over a magnetic stirrer with temperature maintained at 37^{0}C. Samples of 3 ml were withdrawn and replenished immediately from the receiver compartment at 1, 2, 3, 4, 6 and 12hrs. They were stored in refrigerated condition till the analysis was performed. The content of Voriconazole in the samples was analyzed by UV-Visible spectrophotometer. The concentrations of drug were determined Kinetic at 274 nm.

Kinetic modeling of drug release [34]

Mechanism of drug release: Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

A. **Zero order release model:** To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$Q= K_{0\,t}$$

Where, Q= amount of drug released at time t

K_0=zero order release rate constant

The plot of % drug release versus time is linear.

B. First order release model: The release rate data are fitted to the following equation

$$\ln (100\text{-}Q) = \ln100\text{-}\ k_1\ t$$

Where, Q= percent drug release at time t

K_1= first order release rate constant

The plot of log % drug release versus time is linear.

C.Higuchi's Release Model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation

$$Q= K_H\ t^{1/2}$$

Where, Q= percent drug release at time t

K_H= Higuchi's (diffusion) rate constant

In Higuchi's model, a plot of % drug release versus square root of time is linear.

D.Korsmeyer-peppas release model: The release rate data were fitted to the following equation

$$F= (M_t/M) = K_m t^n$$

Where, M_t= drug release at time t

M= total amount of drug in dosage form

F= fraction of drug release at time t

K_m=constant dependent on geometry of dosage form

n=diffusion exponent indicating the mechanism of drug release.

If n is equal to 0.89, the release is zero order. If n is equal to 0.45 the release is best explained by Fickian diffusion, and if 0.45 < n < 0.89 then the release is through anomalous diffusion or non-Fickian diffusion (Swellable& Cylindrical Matrix).In this model, a plot of log (M_t/M) versus log (time) is linear.

RESULTS AND DISCUSSION:
Standard Calibration curve of Voriconazole: It was found that the estimation of of Voriconazole by UV Spectrophotometric method at ʎmax274nm in 6.8 pH buffer had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range,2-10µg/ml.

Construction of calibration curve: The absorbance was measured in uv spectrophotometer at 274nm against 6.8 pH buffer. The absorbances so obtained were tabulated as in table 2. Calibration curve was plotted as shown in figure 2.

TABLE 2. STANDARD CALIBERATION CURVE VALUE OF VORICONAZOLE IN 6.8pH

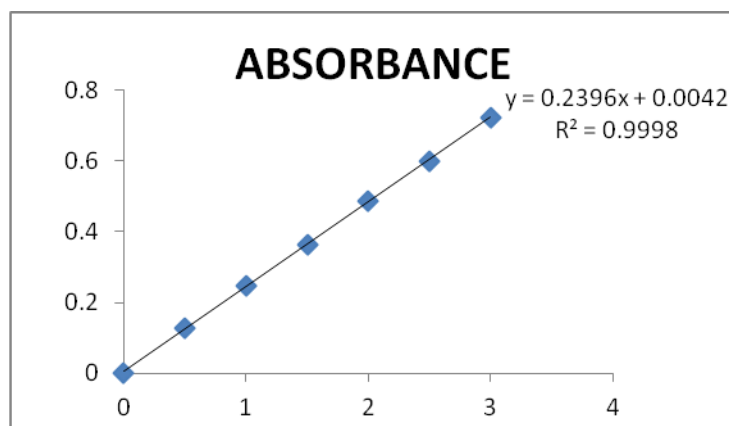| S. No.	Concentration (µg/ml)	Absorbance (at 274 nm)
1	0.5	0.126
2	1	0.248
3	1.5	0.362
4	2	0.487
5	2.5	0.599
6	3	0.723

FIGURE 2. CALIBRATION CURVE OF VORICONAZOLE IN pH 6.8 PHOSPHATE BUFFER

FT-IR spectrum study
The FT-IR spectrum did not show the presence of any additional peaks for new functional groups, indicating no chemical interaction between drug and polymers. The FT-IR were shown in the figure 3-4
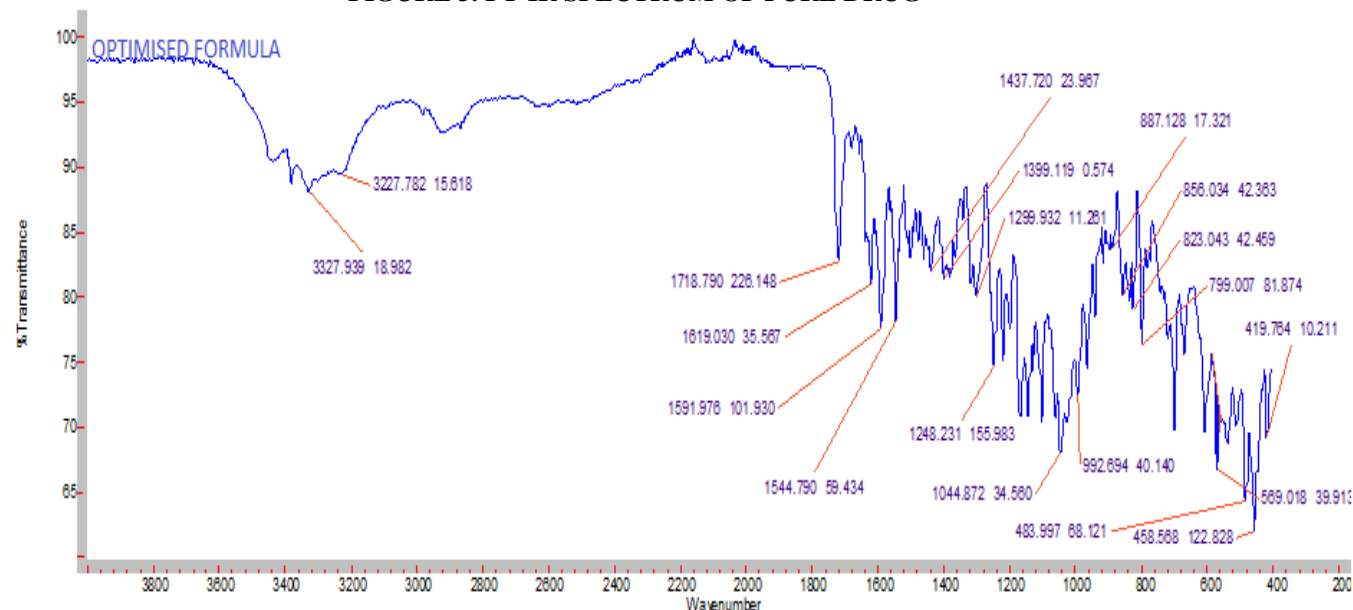

FIGURE 3. FT-IR SPECTRUM OF PURE DRUG

FIGURE 4.FTIR SPECTRUM OF OPTIMIZED FORMULATION
Selection of drug and other ingredients
Voriconazole is selected based on suitability for buccal drug delivery systems, biological and physico chemical properties. Polymers Chitosan Eudragit s 100 were selected.FT-IR studies shown there were no interactions between drug and polymers. Polymers propolylene glycol, tween 80 were selected as permeation enhancer and plasticizer
Formulation of Voriconazole buccal patches:
Buccal patches were prepared by using solvent casting method. The prepared patches were as shown in the figure 5

FIGURE 5 VORICONAZOLE BUCCAL PATCHES

Evaluation of Voriconazole Buccal patches The prepared voriconazole buccal patches were evaluated for physical appearance, flatness, weight variation, thickness, folding endurance, drug content, moisture uptake and moisture content and all the results were found to be with in the pharmacoepial limits as shown in the table 3.

Physical appearance: All the Buccal patches were visually inspected for colour, clarity, flexibility.

Flatness: All the Buccal patches was found to be flat without any foams.

TABLE 3. EVALUATION OF BUCCAL PATCH BY PHYSICAL METHODS

Formulation	Thickness (mm)	Folding Endurance	Drug Content (%)	Moisture Uptake (%)	Moisture Content (%)	Surface pH
F1	0.3432	22	69	14.76	6.02	6.23
F2	0.3287	28	65.8	12.63	5.67	6.17
F3	0.3897	31	79.82	16.68	11.69	5.82
F4	0.3458	29	59.87	18.98	9.76	6.23
F5	0.3218	27	63.42	17.26	6.98	6.73
F6	0.3276	23	57.16	16.25	7.69	6.68

Evaluation of buccal patches by *invitro* permeation studies using dialysis membrane
 The prepared Voriconazole Buccal patches were evaluated for *in vitro* permeation studies using dialysis membrane among all the 6 formulations which contain Chitosan and Eudragit s 100 had shown 95.76 % of cumulative drug release within 12 hours Chitosan Eudragit s 100 shown better drug release profile and the results are shown in table 4.

TABLE.4. EVALUATION OF BUCCAL PATCH BY *IN-VITRO* PERMEATION STUDIES USING DIALYSIS MEMBRANE

Time(hrs)	F1	F2	F3	F4	F5	F6
1	15.66	18.54	28.35	27.89	36.43	16.45
2	34.16	29.73	47.8	36.38	48.18	24.64
4	55.78	35.04	60.24	51.06	59.89	37.11
6	63.01	45.56	68.73	62.52	65.53	47.87
8	72.88	59.25	71.34	78.88	69.43	56.59
10	83.26	69.41	82.17	89.56	79.98	68.34
12	85.35	79.85	89.75	95.76	88.52	71.22

Invitro **permeation studies using dialysis membrane**

Results were plotted to assess the permeation pattern as given in Figure 6 and table 4. All results suggest that the permeation was similar to the *invitro* dissolution studies in most cases and the amount permeated is slightly less than the actual amount of drug dissolved under similar conditions.

TABLE 5. KINETICS OF *IN-VITRO* PERMEATION STUDIES USING DIALYSIS MEMBRANE

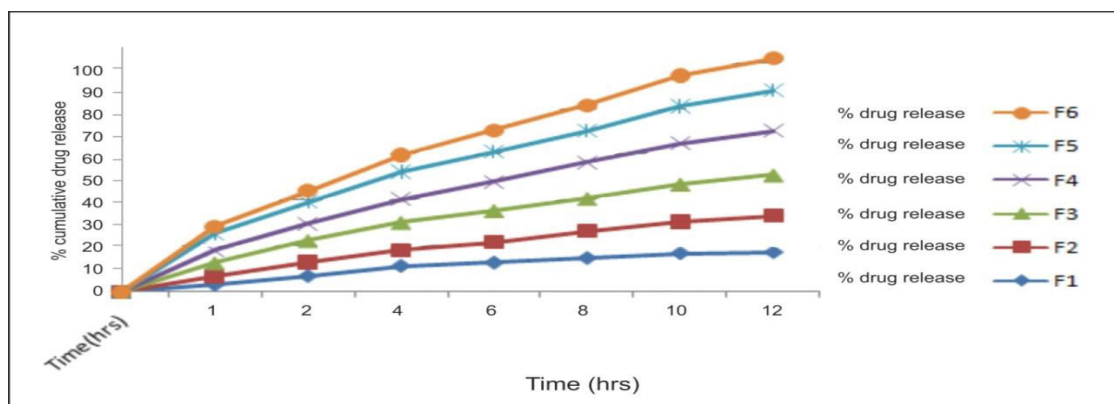| CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN
0	0	0	0	0	0
27.89	1	1.000	1.445	0.000	1.858
36.38	2	1.414	1.561	0.301	1.804
51.06	4	2.000	1.708	0.602	1.690
62.52	6	2.449	1.796	0.778	1.574
78.88	8	2.828	1.897	0.903	1.325
89.56	10	3.162	1.952	1.000	1.019
95.76	12	3.464	1.981	1.079	0.627

FIGURE 6. RELEASE PROFILE OF *IN VITRO* PERMEATION STUDIES USING   DIALYSIS MEMBRANE

Drug release kinetics studies

Table 5 represents the kinetic parameters of *invitro* dissolution studies. The zero order, first order, higuchi diffusion and Korsmeyer-Peppas drawn as represented in figures 7-10.

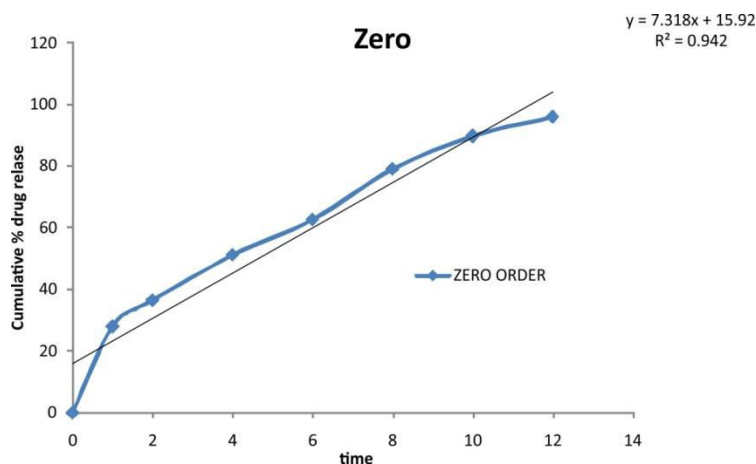Results suggest that the Voriconazole buccal patches could release the drug following first order.

$y = 7.318x + 15.92$
$R^2 = 0.942$

FIGURE 7. ZERO ORDER KINETICS FOR FOR F4 FORMULATION
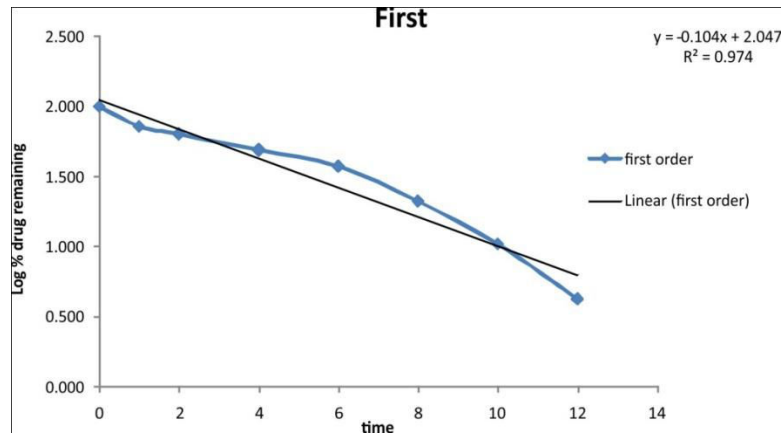
FIGURE 8. FIRST ORDER KINETICS FOR F4 FORMULATION
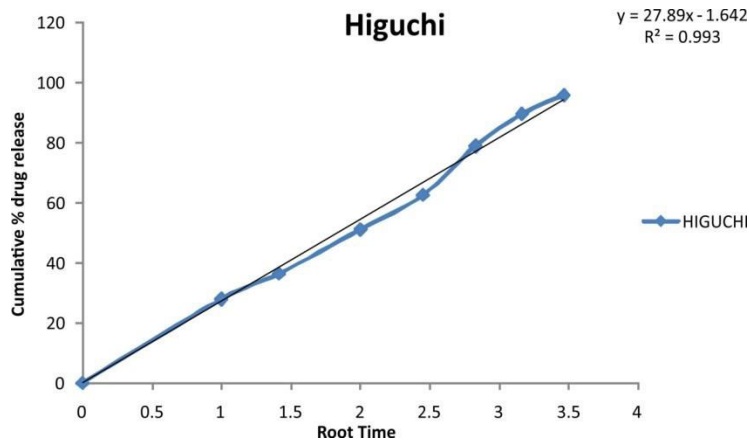

FIGURE 9. HIGUCHI PLOT FOR F4 FORMULATION
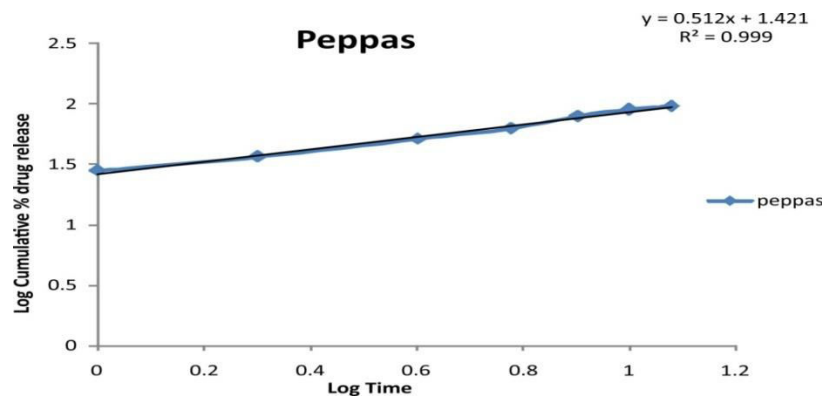

FIGURE 10. KORSEMEYER - PEPPAS PLOT FOR F4 FORMULATION

CONCLUSION:

In present study Matrix type of buccal patches of Voriconazole was developed by using polymers Chitosan and Eudragit S 100. Buccal patches were prepared by employing solvent casting method. Propylene glycol and Tween80 were selected as permeation enhancer and plasticizer. Drug excipient compatibility studies were carried out by using FTIR, and it was observed that there were no interactions. Formulations were prepared with the varying concentrations polymers ranging from F1-F6, and all the formulations were evaluated for various physical parameters Physical appearance, Flatness, Weight

variation, Thickness, Folding endurance, Surface pH, Drug content, Moisture uptake, Moisture content and all the results were found to be were found to be within the pharmacoepial limits, *invitro* drug release studies by using dialysis membrane. Among all the 06 formulations F4 formulation which contain Eudragit S100 100mg had shown 95.76% cumulative drug release within 12 hours. For F4 formulation release kinetics were plotted and the Regression coefficient value was found to be high for Korsemeyer – Peppas model i.e., 0.999.

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