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ABSTRACT

The buccal region offers an attractive site of administration for systemic drug delivery. Risperidone (dose, 1-10 mg) is an anti-psychotic agent whose bioavailability is 70%. Buccal absorption studies of a risperidone solution in human volunteers showed 26.10% drug absorption in 5 min. FT-IR and UV spectroscopic methods revealed that there was no interaction between risperidone and polymers. Risperidone patches were prepared using HPMC (15 & 47 cps), ethyl cellulose, and PVP. The patches were evaluated for their thickness uniformity, folding endurance, weight uniformity, content uniformity, swelling behaviour, percentage moisture loss, tensile strength, percentage elongation, and surface pH. *In vitro* release studies of risperidone-loaded patches in phosphate buffer solution (pH, 6.6) exhibited drug release in the range of 35.64 to 72.33% in 30 min. Data of *in vitro* release from patches were fit to different equations and kinetic models to explain release profiles. Kinetic models used were zero and first-order equations, Hixon-Crowell and Higuchi models. *In vivo* studies in rabbits showed 80.40% of drug absorption from HPMC patches containing PVP while it was 84.59% within 30 min in human volunteers. Good correlation among *in vitro* release and *in vivo* absorption of risperidone was observed. Short-term stability study revealed that drug content decreased in various patches was negligible.

Key words: Risperidone; buccal patches; *in vitro* release; *in vivo* absorption; evaluation

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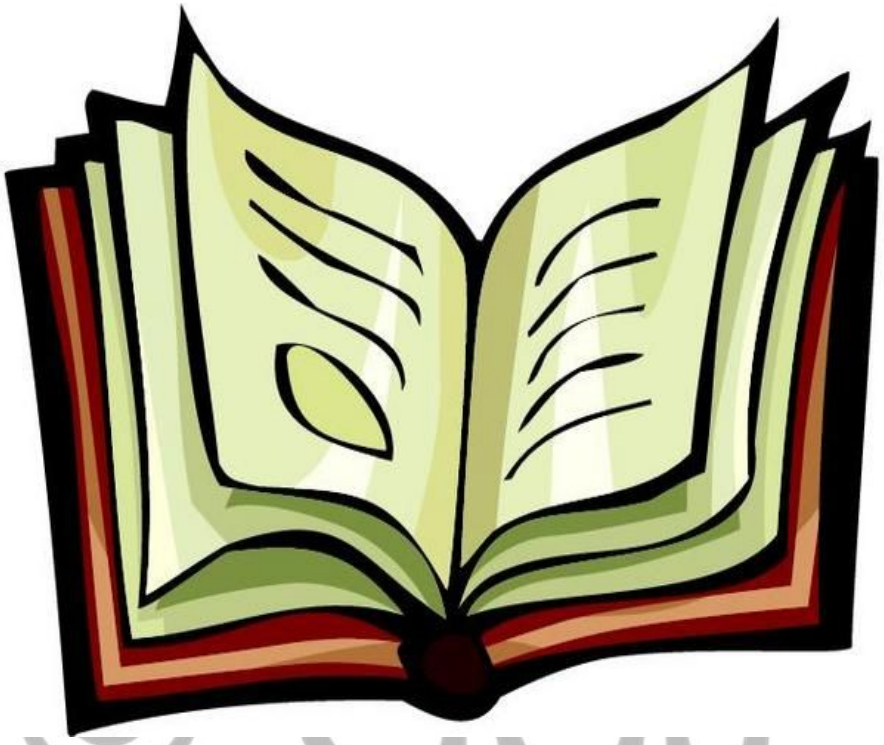


Introduction

INTRODUCTION

For many decades, treatment of an acute disease or a chronic illness has been mostly accomplished by delivering drugs using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols, and injectables as carriers. Amongst various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. However, this route presents some problems for a few drugs. The enzymes in the GI fluids, GIT-pH conditions, and the enzymes bound to GIT membranes are a few factors responsible for the bioavailability problems. The blood that drains the GIT carries the drug directly to the liver leading to first-pass metabolism resulting in poor bioavailability. The inherent problems associated with the drug, in some cases, can be solved by modifying the formulation or by changing the routes of administration. Parenteral, mucosal, and transdermal routes circumvent hepatic first-pass metabolism and offer alternative routes for the systemic delivery of drugs.[1]

The buccal route has the advantage of allowing excellent accessibility, reasonable patient acceptance and compliance, avoids first pass metabolism and involves relatively robust mucosa.[2]

Mucoadhesive drug delivery systems utilize the property of bioadhesion of certain water soluble polymers which become adhesive on hydration and hence can be used for targeting a drug to particular region like gastrointestinal tract, urogenital tract, ear, nose, and eye of the body for an extended period of time.[3]

The oral cavity is highly acceptable by patients. The mucosa is relatively permeable with a rich blood supply; it is robust and shows short recovery times after stress or damage. The virtual lack of Langerhans cells makes the oral mucosa tolerant to potential allergens.[4] The oral transmucosal drug delivery bypasses first pass effect

and avoids pre-systemic elimination in the GI tract. These factors make the oral mucosa a very attractive and feasible site for systemic drug delivery.

Within the oral mucosal cavity, delivery of drugs is classified into the three categories: (1) sublingual delivery, which is delivery of drugs through the mucosal membranes lining the floor of the mouth, (2) buccal delivery, which is drug administration through the mucosal membranes lining the cheeks, and (3) local delivery, which is drug delivery into the oral cavity.

These attributes make the buccal mucosa more suitable for delivery applications. Buccal mucosa also gives rapid absorption of drugs than oral route. A few drugs have been successfully administered via buccal route. For example, buccal buprenorphine works as rapidly as sublingual buprenorphine. Other examples are nicotine, morphine, propranolol, diclofenac sodium, ibuprofen, salbutamol sulphate, carvedilol etc.

Risperidone is a relatively new antipsychotic and is chemically, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro- 4H- pyrido [1,2-a] pyrimidin-4-one. The apparent half-life of risperidone is 3 hours and its absolute oral bioavailability is 70%. Excretion is mainly in the urine and, to a lesser extent, in the faeces. Risperidone and 9-hydroxyrisperidone are about 90 and 77% bound to plasma proteins, respectively. It's daily oral dose is 0.5 to 10 mg per day in divided doses. [5,6]

SCHEME OF WORK:

PHASE-I:

1. Extensive literature survey

2. Fabrication of glass substrates.

PHASE-II:

1. Formulation and design of polymeric patches.

2. Preliminary physical evaluation of polymeric patches.

3. Selection of best composite based on preliminary physical evaluation.

4. Preformulation studies.

PHASE-III:

Evaluation of selected polymeric patches:

1. Physical Evaluation:

i) Mean thickness

ii) Swelling index

iii) Moisture loss

iv) Folding endurance

2. Mechanical Evaluation:

i) Tensile strength

ii) Elongation at break

3. Bioadhesive strength

PHASE-IV:

1. Incorporation of risperidone in selected polymeric patches.

2. Evaluation of risperidone polymeric patches for:

i) Content uniformity

ii) *In vitro* release

iii) *In vivo* studies

PHASE-V:

1. Kinetics studies

2. Interpretation of data

3. Conclusion.

Objectives

OBJECTIVES

The absorption of drugs through the oral mucosa improves bioavailability of drugs that might otherwise be metabolized by first-pass effect (pre-systemic drug elimination) during their passage through the gastrointestinal tract. Drug absorption from the oral mucosa is mainly via passive diffusion through the lipoidal membrane. Thus, oral mucosal route of drug delivery has attracted the attention world wide for optimizing the drug delivery.[1]

The objectives of the present investigation are**:**

To develop analytical method for the estimation of risperidone in a suitable solvent system.

To carry out preformulation studies for the drug, polymers, and blends.

To design a suitable buccal mucoadhesive delivery system (films) for risperidone using mucoadhesive polymers.

To evaluate the dosage forms (films) for the integrity and stability.

To study *in vitro* release of drug from the dosage forms.

Preliminary studies on *in vivo* absorption for a short time.

Several polymers have been identified for mucoadhesive properties. In the present investigation, HPMC-15cps, HPMC-47cps, ethyl cellulose, and poly vinyl pyrrolidone (PVP) were used.

The drug chosen for the present investigation is risperidone, an anti-psychotic agent. More than half of an oral dose of risperidone is reported to be absorbed. Following oral administration, the apparent mean terminal elimination half-life of risperidone is

3 hours. Peak Plasma concentrations achieved after 1 to 2 hours of the oral administration.[4]

Rationale of Drug Selection

In general, rapid absorption of drugs from the buccal mucosal route is observed because of thin mucous membrane and rich blood supply. A drug is considered to be a suitable candidate for buccal mucosal delivery, if the following conditions are satisfied.

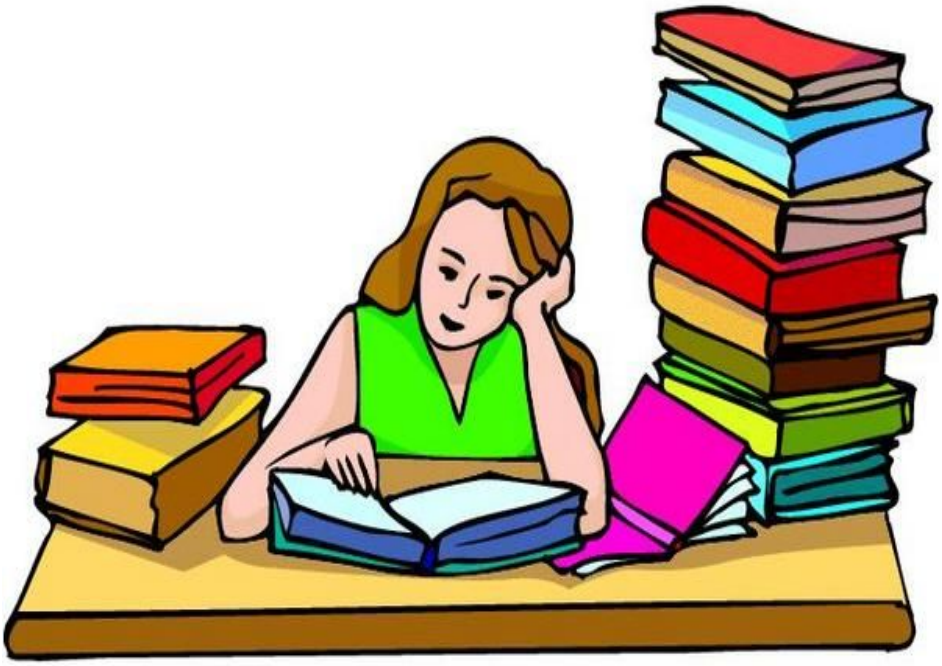
The prescribed dose of the drug should be low. Any drug with a daily requirement of 25 mg or less would be a candidate suitable for buccal delivery. Though the prescribed dose of risperidone is 10 mg daily, selected dose for the patch is 1 mg. Therefore, it is possible for the drug to get absorbed in a short time and safe for animal study.

The bioavailability of the drug should be low or variable. For the risperidone, it is about 70%.[6] Therefore, this drug is suitable for buccal absorption.

The t_{max} of risperidone is 1-2 hours by peroral route, which is variable.[5] Therefore, a route facilitating rapid absorption should be explored. As a result, buccal route is attempted in this thesis.

The p*K*a of the drug should be ideally greater than 2 for an acid and less than 10 for a base. Risperidone is a weak base and its p*K*a value is approximately 7.89 .

From the above points, it is clear that risperidone is a suitable drug for the buccal absorption and may provide a better therapeutic profile than that of the oral route.



Review of Literature

REVIEW OF LITERATURE

The oral mucosa has been studied extensively as a potential route for systemic drug delivery. Early oral mucosal drug delivery work focused on the phenomenon that drugs could be absorbed via the oral mucosa. This interest had diminished somewhat with the finding that only a few drugs are clinically needed and practically feasible to be delivered via the oral mucosal route. More recently, interest has been renewed with the finding that certain penetration enhancers are effective in improving the permeability of oral mucosal tissue, coupled with more appropriate ways to deliver drug to this site, for example, buccal patches, chewing gum, bioadhesive tablets etc.

Advantages of Drug Delivery through Buccal Mucosa

It permits easy accessibility.

It is a passive system and does not require activation.

Enzymatic activity is very low as compared to stomach.

It bypasses hepatic first-pass metabolism, prevents gastric acid lability, thus increases bioavailability of drug.

Buccal mucosa is highly perfused with blood vessels and offers greater permeability than skin.

Easy of administration and it can be easily removed in case of emergency

Therapeutic serum concentration can be achieved rapidly.

The drug delivery system (film) can be made unidirectional to ensure only buccal absorption.

Drugs showing poor and low absorption in the stomach can be given by this route.

It can be made unidirectional to ensure only buccal absorption.

Patients with an upper gastrointestinal tract disease or surgery which affects oral drug absorption or those who have difficulty in swallowing peroral medications, the buccal cavity may be a useful site for drug delivery.

The presence of saliva ensures relatively large amount of water for drug dissolution unlike in case of rectal and transdermal routes.

The oral mucosa lacks prominent mucus secreting goblet cells and therefore there is no problem of diffusion limited mucus build up beneath the applied dosage form.

It allows for the local modification of tissue permeability, inhibition of protease activity or reduction in immunogenic response. Thus, selective uses of therapeutic agents like peptides, proteins and ionized species can be achieved.

Limitations of Drug Delivery through Buccal Mucosa

Drug that is impermeable to the oral mucosa cannot be used.

Surface area available for absorption is less.

Patient may swallow the patch.

Eating and drinking are restricted until complete absorption has taken place, so these drug delivery systems should be fast releasing systems.

It may be difficult to convince the patient because of unpleasant taste, odour and irritability to the mucosa.

The drug should be stable at buccal pH.

The buccal mucosa is relatively less permeable than the small intestine, rectum, etc.

This route can administer those drugs, which are absorbed by passive diffusion.

A drug with small dose requirement is must.

To the pharmacist interested in oral drug delivery, the mucosa of the mouth may appear to differ little from the rest of the moist lining of the gastrointestinal tract. The use of the oral mucosa for drug delivery has led to the tendency at least in the dermatological literature, to regard oral mucosa as a highly permeable tissue.

Thimmasetty *et al*.[7] prepared and evaluated buccal dosage forms of insulin. The prepared films were subjected to thickness, weight uniformity, content uniformity, *in vitro* diffusion studies, and *in vivo* studies. It was found that the release rate of insulin was higher from buccal films made with sod. CMC and HPMC.

Amir H[8] Shojaei explained in detail about buccal mucosa and various drug delivery systems used for systemic action across the oral mucosa. Authors also explained in detail about the structure and composition of buccal mucosa. He also discussed the various methods of buccal permeation studies, various methods for buccal permeation enhancement and designing of various buccal drug delivery systems for systemic drug delivery.

Rinku K *et al.* developed mucoadhesive films of miconazole nitrate using HPMC, HPC, carbopol 934P, and glycerol as a plasticizer. [9] In this study films are prepared

by casting procedure using various polymer compensations and were evaluated for their *in vitro* bio adhesive performance and release characteristics. The result showed the *in vitro* adhesion time and release behavior were found to be function of type of polymer used.

Hirokazu *et al.*[10] developed polymer film dosage forms of lidocaine for buccal administration. In this study, they examined the penetration rate of lidocaine. The result shows a significant relationship between the penetration rate of lidocaine and release rate of unionized lidocaine.

Luana P *et al.*[11] formulated mucoadhesive patches for buccal administration of ibuprofen. A new formulation for topical administration of drugs in the oral cavity has been developed using several film forming and mucoadhesive polymers. The films have been evaluated for swelling studies, mucoadhesion, organoleptic characteristics and *in vitro* release revealed that the diffusion process was the main drug release mechanism and higuchi models provided the best fit. *In vivo* studies showed presence of ibuprofen in saliva for 5hrs. No irritation was observed after administration.

Pavan *et al.*[12] prepared buccal films of salbutamol sulphate using different polymer like ethylcelluose, HPMC, and eudragit RL-100. The drug release studies indicated the first order kinetics in all cases and release was extended up to 8 h. It was also observed that lower the permeability co-efficient the grater was the extend release charters tics for buccal films.

Panigrahi *et al.*[13] designed and characterised mucoadhesive buccal patches of diclofenac sodium using non-ionic polymers, poly vinyl alcohol and hydroxyl ethyl cellulose and chitosan as cationic polymer. The result showed an increase in radial

swelling after addition of diclofenac sodium to the plain formulation. A decrease in residual time observed for poly vinyl alcohol and chitosan containing formula. High degree release was obtained from poly vinyl alcohol compared to the hydroxyethylcellulose. Physical characteristics of the studied patches showed promising results with good bioadhesion.

Nazila SM *et al.*[14] reviewed that mucoadhesive polymers used in the buccal drug delivery. Authors explained about the structure of oral mucosa, mucoadhesion theories involved in the mucoadhesion and mucoadhesive dosage forms for buccal administration.

Ryan FD *et al.*[15] designed bioadhesion patch for dose controlled topical delivery of imiquimod by using copolymer of methyl vinyl ether and maleic anhydride (PVME/MA) and tripropylene glycol methyl ether as plasticizer. Patches containing imiquimod shows *in vitro* release over a period of 6 h.

Shafiullah D *et al.*[16] prepared chitosan buccal films and gels containing chlorhexidine gluconate. Chitosan films were prepared using solvent casting technique. Films were evaluated for thickness, swelling index, tensile strength, content uniformity and *in vitro* release of chlorhexidine. Gels were evaluated for viscosity, mucoadhesive strength and drug release. *In vitro* drug release was sustained up to 4 hours, which can be advantageous for periodontal disease treatment.

Diojad *et al.*[17] studied buccoadhesive drug delivery system of isosorbide dinitrate using carbopol 934P, HPMC, and eudragit RL-100 as polymer and propylene glycol as a plasticizer. The results indicated that, the therapeutic level of isosorbide dinitrate can be achieved using this buccal adhesive formulation.

Thimmasetty J *et al.*[18] designed and evaluated of fexofenadine HCl buccal mucoadhesive patches. In this study a number of buccal mucoadhesive patches of fexofenadine HCl were prepared by casting method using HPMC (15cps) polymer and co-polymer such as carbopol 934, eudragit RS 100, and ethyl cellulose. *In vivo* buccal absorption studies in rabbits showed 60.17 and 63.14% of drug release from HPMC-eudragit and HPMC patches, respectively. *In vivo* patch test in human volunteers revealed that 66.98 to 84.76% of drug was absorbed within 20 min. *In vitro* release and *in vivo* absorption for all patches followed zero order and exhibited good correlation among them.

Mona S *et al.*[19] prepared mucoadhesive buccal films of glipizide using HPMC, sodium CMC, carbopol-934P, eudragit RL-100, and evaluated for weight, thickness, *in vitro* residence time, swelling index, surface pH, *in vitro* release, permeation studies and content uniformity, the films exhibited controlled rerelease over more than 6 h.

Perumal *et al.*[20] prepared and characterized the monolayered multiploymeric films containing propronalol hydrochloride using eudragit-100 and chitosan. The prepared films showed in the *in vitro* release up to 8 hours and release mechanism followed higuchi square root model.

Thimmasetty J *et al.*[21] studied mucoadhesive patches for buccal administration of carvedilol. Buccal absorption studies of a carvedilol solution in human volunteer showed 32.86% drug absorption. FT-IR and UV spectroscopic method revealed that there was no interaction between carvedilol and polymers. Carvedilol patches were prepared using HPMC, carbopol 934, eudragit RS 100 and ethyl cellulose. Results showed a good correlation among *in vitro* release and *in vivo* release of carvedilol.

Table 01: Commercially available drug delivery systems for systemic delivery by the oral mucosal route.[22]

Mucosal site	Drug	Dosage form
Buccal	Propranolol	patch-SR
	Lorazepam	lyophilized tablets
	Verapamil HCl	sustain release tablets
	Oxazepam	lyophilised tablets
	Prochlorperazie	bioadhesive tablets and solutions
	Nicotine	chewing gum
Sublingual	Nitroglycerine	Tablets, sprays, bioadhesive tablets
	Buprenorphine	Tablets
	Nifedipine	Tablets

Oral cavity: Anatomic and Physiologic Features [23]

The oral cavity presents a surface area of about 100 cm^2. The thickness of buccal mucosa is measured to be 500-800 μm.

Three different types of oral cavity are recognized,

Lining mucosa

Masticatory mucosa

Specialized mucosa

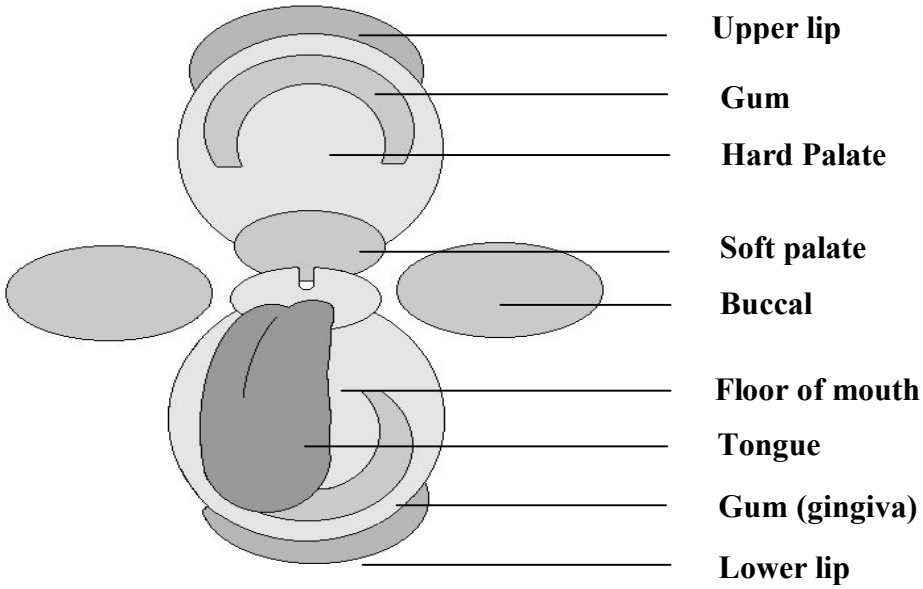


Figure 1: Schematic representation of oral mucosa

Lining mucosa (60% of total oral mucosa) is 500-800 μm in thickness and covers lips, cheeks, soft palate, lower surface of tongue and floor of the oral cavity.

Masticatory mucosa representing 25% of total oral mucosa is 100-200 μm in thickness and covers the gingival and hard palate. It is tightly attached to underlying structure and subjected to abrasion and shear stress during mastication.

The specialized mucosa (15% of total oral mucosa) is found on dorsum of tongue and involved in taste.

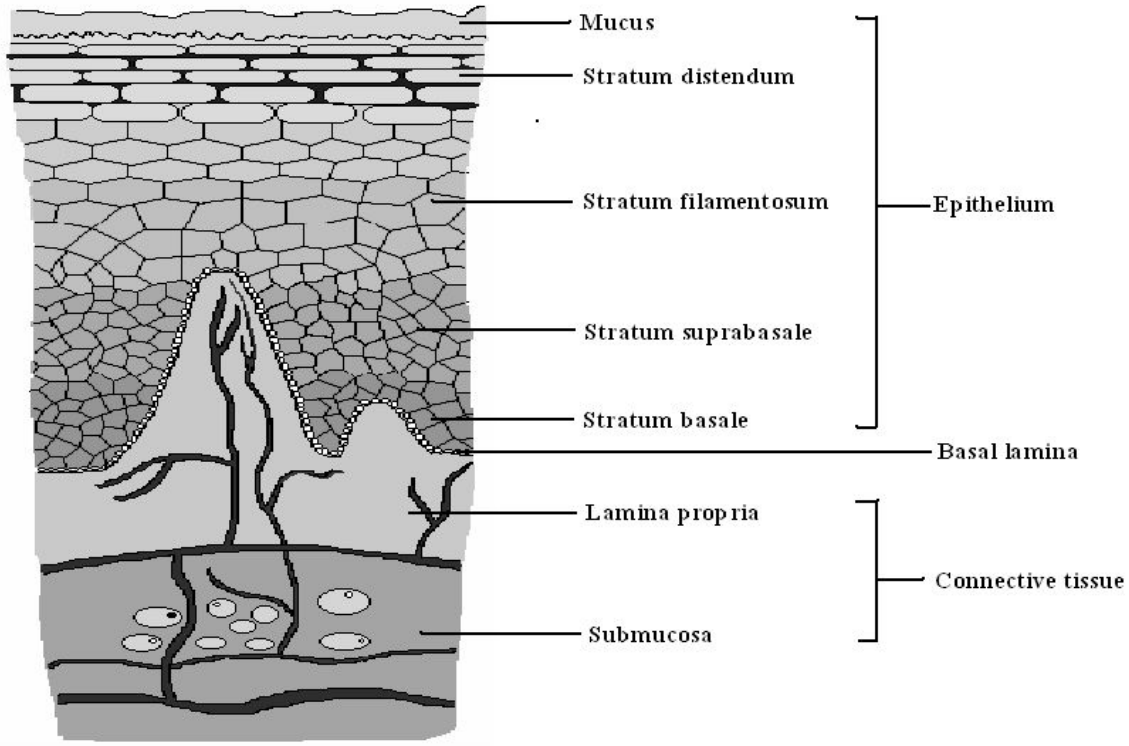


Figure 2: Cross section of oral mucosa

The term buccal refers to lining of cheek, upper and lower lips which represents one third of total oral mucosa surface. Buccal mucosa composed of several layers of different cells.

The epithelia is similar to stratified squamous epithelia found in rest of body and is about 40-50 cell layers thick. Lining epithelium of buccal mucosa is the nonkeratinized stratified squamous epithelium has thickness of approximately 500-

600 μ and surface area of 50.2 cm^2. Basement membrane, lamina propia followed by submucosa is present below epithelial layer. Lamina propia is rich with blood vessels and capillaries that open to internal jugular vein.

Functions of Buccal Epithelium

Protection of underlying tissue.

In non keratinized regions, lipid based permeability barriers in outer epithelial layers protect the underlying tissues against fluid loss.[3]

Functions of Oral Cavity

As a portal for intake of food material and water.

Lubrication of food material.

Identification of ingested material by tastebuds of tongue.

To aid in speech and breathing process.

Initiation of carbohydrates and fat metabolism and absorption of catabolic products after metabolism.

To bring chewing, mastication and mixing of food stuff.

Secretions of Oral Cavity

Saliva: Saliva is complex fluid containing organic and inorganic materials. It is produced by three pairs of major glands viz, parotid, submandibular and sublingual glands situated in outside the oral cavity and in minor salivary glands situated in tissues lining most of the oral cavity. The surface of oral cavity is constantly bathed with a stream of saliva approximately 1litre/day by salivary glands. The pH of saliva varies from 6.5 to 7.5. It has a low buffering capacity and principal buffer of saliva being bicarbonate. Chemically saliva consists of

99.5% water

0.5% solutes.

Solute includes sodium, potassium, calcium, phosphate, bicarbonate, chloride, urea, uric acid, serum albumin, mucin, enzymes and dissolved gases.

Physiological functions of saliva

Modulation of oral mucosa

Remineralisation of teeth with calcium phosphate salts.

Neutralization of acid in oral cavity.

Stimulation of epithelial proliferation.

Initiation of fat and starch digestion.

Lubrication and cleansing if oral, pharyngeal and oesophageal mucosa.

Cervicular fluid: It is a fluid secreted from gingival glands of oral cavity.

Mucus: Mucus is a thick fluid composed of mainly of water, electrolytes and a mixture of several glycoproteins. Mucus is secreted in buccal cavity which helps to produce saliva. It protects biological membranes and acts as excellent lubricant.

The oral cavity may be divided into two regions, the outer oral vestibule, bounded by the lips and cheeks and the oral cavity itself the borders being, and formed by the hard and soft palates, the floor of the mouth and tonsils.

Table 02: Regional variation in the composition of oral mucosa

Tissue	Structure	Epithelial Thickness (µ m)	Residence time	Blood flow (ml/min/cm^2)
Buccal	Non-keratinized	500-600	+	2.40
Sublingual	Non-keratinized	100-200	--	0.97
Gingival	Keratinized	200	+	1.47
Palatal	keratinized	250	--	0.89

Although blood flow through oral mucosa of humans has not been reported, but it is generally considered that the blood flows through human oral mucosa, even during disease, is sufficiently fast as not to be rate limiting factor in the absorption of drugs via the oral mucosa.

Muco/Bioadhesion [3]

According to Longer and Robinson, the attachment of synthetic or natural macromolecule to mucus (mucoadhesion) or an epithelial surface (Bioadhesion).

Theories of muco/Bioadhesion

Many theories have been proposed to explain the forces that underpin bioadhesion. They are,

1) Electronic theory: In this theory different electronic property of the mucoadhesive polymer and the mucus glycoprotein, electron transfer between these two surface occurs. Electron transfer contributes to formation of a charged double layer at the interface of the mucus and the polymer, which results in forces of attraction in this region and interdiffusion of the two surfaces.

2) Adsorption theory: The primary and secondary chemical bonds of the covalent and non-covalent (electrostatic, vander walls' forces, hydrogen and hydrophobic bonds) types are formed upon initial contact between the mucus and the mucoadhesive polymer. Most of the initial interfacial bonding forces is attributed to non covalent forces.

3) Wetting theory: The ability of a bioadhesive polymer to spread on biological surfaces. This theory is predominantly applicable to liquid bioadhesive systems. Moderately wettable polymers have been shown to exhibit optimal adhesion to human endothelial cells.

4) Diffusion theory: The basic involved in this theory is chain entanglement between glycoproteins of the mucus and mucoadhesive polymer. Upon initial contact between these two polymers, diffusion of the bioadhesive polymer chain into the mucus network creates an entangled network between the two polymers. Sufficient polymer chain flexibility, adequate exposure for the surface contact of both polymers, similar chemical structures, and the diffusion coefficient of the bioadhesive polymer are among the factors which influence the interdiffusion of the macromolecule network.

5) Fracture theory: It relates the force required for the detachment of polymers from mucus to the strength of their adhesive bond. It has been found that work fracture is greater when the network strands are longer or the degree of cross-linking is reduced.

Factors Affecting Mucoadhesion in Oral Cavity

A variety of factors affect the mucoadhesive properties of polymers, such as molecular weight, flexibility, hydrogen bonding, charge, concentration and swelling of a polymer.

Polymer Related Factors

1) Molecular weight: In general, it has been shown that the bioadhesive strength of a polymer increases with molecular weights above 1, 00,000.

2) Flexibility: Bioadhesion starts with the diffusion of the polymer chains in the interfacial region. Therefore, it is important that the polymer chains contain a substantial degree of flexibility in order to achieve the desired entanglement with the mucus. In general, mobility and flexibility of polymers can be related to their viscosities and diffusion coefficients, where higher flexibility of a polymer causes greater diffusion into the mucus network.

3) Charge: Peppas and Buri have demonstrated that strong anionic charge on the polymer is one of the required characteristics for mucoadhesion. The nonionic polymers appear to undergo a smaller degree of adhesion compared to anionic polymers.

4) Hydrogen bonding: It is another important factor in mucoadhesion of a polymer. Park and Robinson found that in order for mucoadhesion to occur, desired polymers must have functional groups that are able to form hydrogen bonds. They have also confirmed that flexibility of the polymer is important to improve this hydrogen bonding potential.

5) Concentration: The importance of this factor involved in the development of a strong adhesive bond with the mucus, and can be explained by the polymer chain length available for penetration into the mucus layer. When the concentration of the polymer is too low, the number of penetrating polymer chains per unit volume of the mucus is small, and the interaction between polymer and mucus is unstable. In general, the more concentrated polymer would result in a longer penetrating chain length and better adhesion.

6) Hydration: Hydration is required for a polymer to expand and create a proper "macromolecular mesh" of sufficient size, and also to induce mobility in the polymer chains in order to enhance the interpretation process between polymer and mucin. However, a critical degree of hydration of the mucoadhesive polymer exists where optimum swelling and bioadhesion occurs.

Environmental Factors

The mucoadhesion of a polymer not only depends on its molecular properties, but also on the environmental factors adjacent to the polymer. Saliva, as a dissolution medium, affects the behavior of the polymer. pH of the microenvironment surrounding the

mucoadhesive polymer can alter the ionization state. Mucin turnover rate is another environmental factor. The residence time of dosage forms is limited by the mucin turnover time, which has been calculated to range between 47 and 270 min in rats and 12-24 h in humans.

Movement of the buccal tissues while eating, drinking, and talking, is another concern which should be considered when designing a dosage form for the oral cavity. Movements within oral cavity continue even during sleep, and can potentially lead to detachment of the dosage form. Therefore, an optimum time span for the administration of the dosage form is necessary in order to avoid many of these interfering factors.

Drug Transport Across the Oral Mucosa [24, 25]

Recent research attention is on understanding the biological and physicochemical nature of drug absorption process and mechanism of drug penetration across the tissue at cellular and molecular level. The coexistence of the hydrophilic & lipophilic regions in the oral mucosa suggests that there are two routes for drug transport i.e., paracellular and transcellular routes.

The paracellular route is the primary route for hydrophilic compounds. It involves passage between cells through cellular lipid material of intercellular spaces.

The flux of drug movement in this route J_H can be written as,

$$J_H = \frac{D_H \varepsilon * C_D}{h_H}$$

Where,

ε – Fraction of surface area of paracellular route

D_H – Diffusion coefficient in intercellular spaces

h_H – Path length of paracellular route

C_D – Donor side drug concentration

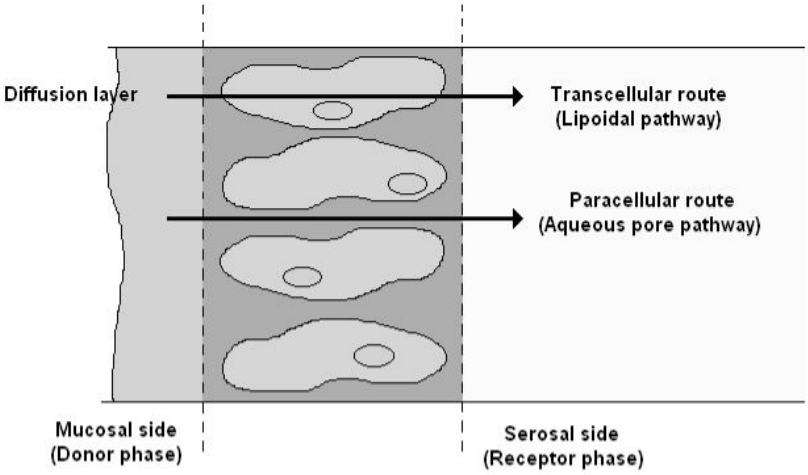


Figure 3: Drug absorption pathways across buccal mucosa

This route is a tortuous one, requiring the epithelium to have a sufficiently open matrix and drug to have an appreciable affinity and diffusivity in the intercellular fluids.

For lipophilic compounds, because the surface area for the transcellular route is large, the partition coefficients are high, and the pathlength for transcellular movement is relatively short, the permeability of lipophilic compounds across the epithelial cell membrane is typically high. In this case, drug molecules have to move across lipophilic cell membrane and hydrophilic cytoplasm as well as intercellular space. Since the main resistance of this route is the cell membrane, drug movement in the cytoplasm and intercellular space is relatively rapid and assumed as instantaneous.

Therefore the drug flux in the transcellular route can be expressed as,

$$J_L = \frac{(1-\varepsilon)D_L K_P * C_D}{h_L}$$

Where,

K_P – Partition coefficient between lipophilic and hydroliphic region

D_H – Diffusion coefficient in intercellular spaces

h_L – Pathlength of transcellular route

C_D – Donor side drug concentration

This equation also shows that the permeability coefficient through the transcellular route is proportional to the partition coefficient.

The paracellular and transcellular routes depicted here are a simplified version of the oral mucosal drug absorption process. From a dynamic point of view, drug molecules will preferentially move through the route which offers the least resistance. Since the movement of drug molecules may involve a mixture of these two routes, i.e., using one route in one region and other route in the other region.

Buccal Mucoadhesive Dosage Forms

Buccal adhesive dosage forms can deliver the drug either locally to treat condition within the buccal cavity or systemically via the mucosa. It is often a requirement that buccal adhesive dosage forms should adhere and allows controlled delivery of drug for prolonged periods. Buccal adhesive dosage form can be divided into following types viz,

Tablets

Patches/films

Semisolids

Powders

Buccal Tablets: Buccal tablets are small, flat, and oval with a diameter of approximately 5-8 mm. Unlike conventional tablets, buccal mucoadhesive tablets allow for drinking and speaking without major discomfort.

The saliva softens the buccal tablets which is adheres to mucosa, and is retained in position until dissolution or release is complete. These tablets can be applied to different sites in the oral cavity, including the palate, the mucosa lining the cheek, as well as between the lip and gum. Successive tablets can be applied to alternate sides

of the mouth. The major drawback of buccal bioadhesive tablets is their lack of physical flexibility, leading to poor patient compliance for long term and repeated use.[14]

Semisolid preparations: Bioadhesive gels or ointments have less patient acceptability than solid dosage adhesive forms and most are used only for localized drug therapy within oral cavity. One of the original oral mucosal adhesive delivery system- "orabase" consists of finely ground pectin, gelatin and sodium CMC dispersed in poly(ethylene) and mineral oil gel base, which can be maintained at its site of application for 15-150 min.[2]

Powders: Yama moto *et al* have been described a hydroxypropyl cellulose and beclomethasone dipropionate containing powder that was sprayed onto oral mucosa of rats. A significant increase in residence time relative to an oral solution was seen and 2.5% of beclomethasone was retained on buccal mucosa for over 4 h.

Buccal Mucoadhesive Patches

These are two ply laminates or multilayered thin film, round or oval consistently basically of bioadhesive polymeric layer and impermeable basically layer to provide unidirectional flow of drug across buccal mucosa.

Design of Buccal Mucoadhesive Patches [26]

The following consideration are taken while designing buccal mucoadhesive patches

Convenient to apply and unobtrusive when in place.

Not to incorporate a bitter tasting drug.

It should have smooth surface rather than textured surface.

Preferably it should achieve unidirectional release of drug.

It should not irritate buccal mucosa.

The different components of buccal mucoadhesive patches are,

1) Drug: The important drug properties that affect its diffusion through the patch as well as buccal mucosa include molecular weight partition coefficient, dissociation constant of drug. The selection of suitable drug to design buccal drug delivery system is based on pharmacokinetic properties.

Following are the properties for candidature to mucoadhesive buccal drug delivery system.

Conventional dose of drug should be less.

The drug should not adversely affect the natural microbial flora of oral cavity.

Drug should not have bad taste and free from irritancy, allerginicity, discolouration or erosion of teeth.

2) Buccal adhesive polymers: Polymer is a very long molecule consisting of structural units connected by covalent chemical bonds. Bioadhesive formulations use polymers as adhesive component. These formulations are often water soluble and when in dry form attract water from biological surface and this water transfer leads to strong interaction. These polymers also form viscous liquids when mixed with water. Bioadhesive polymers should possess certain physicochemical feature including hydrophilicity, hydrogen bonding and visco-elastic properties.

3) Plasticizer: These are the materials used to achieve softness and flexibility of thin films of polymer or blend of polymers. The plasticizer which helps in release of drug

from polymer base as well as it acts as penetration enhancer. Usually the concentration of polymer will be the 10-50% of the total polymer weight.

Ex: glycerol, Propylene glycol, PEG-200, PEG-400.

4) Permeation enhancer: The substances that facilitate the permeation through buccal mucosa are referred as permeation enhancers. Most of the permeation enhancers were designed for purposes other than absorption enhancement, a systemic search for safe and effective penetration enhancers must be priority in drug delivery. The selection of enhancer and its efficacy depends on physicochemical properties of drug, site of administration, nature of vehicle and other excipients.

The different permeation enhancers available are,

Chelators: EDTA, citric acid, sodium salicylate, methoxy salicylates.

Surfactants: sodium lauryl sulphate, polyoxyethylene, cetylpyridinium chloride.

Bile salts: sodium glycoholate, sodium deoxycholate, sodium taurocholate.

Fatty acids: oleic acid, capric acid, lauric acid, propylene glycol, methyloleate, phosphatidylcholine.

Non-surfactants: unsaturated cyclic ureas.

Inclusion complexes: cyclodextrins.

Thiolated polymers: chitosan-cystiene, poly-homocystiene, polycarbophil-cystiene/GSH, chitosan-4-thioglycholic acid.

5) Backing membrane: It is also one component which provides unidirectional drug flow to buccal mucosa. It prevents the drug to be dissolved in saliva and hence swallowed avoiding the contact between drug and saliva. The thickness of backing

membrane must be around 75-100 μ. The material used for backing membrane must be inert and impermeable to drugs and penetration enhancers.

Ex: ethyl cellulose, Cellophane-325, Polyglassine paper.

Evaluation

In Vitro Methods

Beaker method: The dosage form in this method is made to adhere at the bottom of the beaker containing the medium and stirred uniformly using overhead stirrer. Volume of the medium used in the literature for the study varies from 50-500 ml and the stirrer speed from 60-300 rpm.[08]

Many laboratory animals have been tested for *in vitro* oral mucosa permeability studies. The most commonly used animals are dogs, rabbits, hamsters, pigs, Rhesus monkeys, guinea pigs, rats etc. The oral mucosa of dogs, pigs, rabbits and Rhesus monkeys are believed to be similar to human oral mucosa because the epithelia are nonkeratinized.[07]

In vitro permeability coefficients of tritiated water in human and pig oral mucosa, buccal and floor of mouth have been reported to be similar.[11]

Dissolution apparatus: Standard USP or BP dissolution apparatus have been to study *in vitro* release profiles using both rotating elements paddle, and basket. Dissolution medium for the study varied from 100-500 ml and speed of rotation from 50-100 rpm.[23]

Other methods: Other methods involve plexiglass sample blocks placed in flasks, agar gel method, Valia-Chien cell, USP Type 2 dissolution apparatus, etc.

Although a number of methods have been reported, the ideal method would be one where sink condition is maintained and dissolution time *in vitro* simulates dissolution time *in vivo*.

In Vivo Methods

The most desirable *in vivo* approach is to perform experiments in human volunteers or patients. However, it is very difficult to begin with this approach, because of the difficulties of cost, time and toxicity of drug and ethical considerations. Therefore, animal models are being usually used for this purpose.

The most important and difficult aspect of the experimental design is the choice of animal species. Animal models such as dog, cat, rabbit, rat and sheep have been used to determine the oral mucosal absorption characteristics of drugs.

Very few, and certainly no extensive *in vivo* (animal) *in vivo* (human) correlation have been reported, which would allow us, to compare the oral mucosal absorption characteristics of a particular animal with those of its human counter part. However, the methods used in *in vivo* studies are absorption cells and perfusion cells.

Disc methods: These methods have advantage that the absorption across a defined oral cavity mucosa can be studied. A polymer disc with a diameter of approximately 3.5 cm and height of 1 cm was used in a study. The disc had a central depressions depth of 4 mm. A water soaked filter paper disc was placed in the depression and known amount of drug spread onto it. Once the drug had dissolved the device was placed onto defined oral mucosal surface and maintained in place for 5 min. After removal, a non-impregnated disc was used to wipe the oral mucosa, the discs combined and analysed.

Disc techniques allow investigators to study drug loss across a fixed area defined oral cavity membrane. Major limitations of the technique include adherence of the disc to the membrane, leakage of drug form the disc and interference from salivary secretions.

Absorption cells: Absorption cells are defined as those techniques which restrict known volumes of an aqueous test solution to a defined area of oral mucosa. The cell can be open or closed in the oral environment, but in either case, the test solution within the cell is protected from salivary secretions, and, therefore, volume does not change.

In this method used a rubber **'O-ring'** with an internal diameter of 2.64 mm which was fixed to the mucosa using a cyanoacrylate adhesive. [21] The cell was filled with 10 µl of buffered test solution and the absorption characteristics of the organic solutes were determined by taking plasma samples and samples of the test solution in the 'O-ring'.

This method involving a **"Cup"** which exposed a surface area of 2.2 cm^2 to investigate the absorption characteristics of a novel angiotensin converting enzyme (ACE) across the buccal mucosa of anesthetized dogs.

Perfusion cells for animal studies: Veillard developed the perfusion cell, which was made from a medical grade silicon polymer. The cell had a volume of 0.075 cm^3 and exposed area of 0.25 cm^2. Barshun constructed a pliable cell made of a hydrophilic vinyl polysiloxane polymer which had an internal volume of 1 ml and allowed a 1.8 cm2 area of buccal membrane to be perfused. The design also incorporated sealing lip to prevent leaks. Ranthbone reported a buccal perfusion cell design constructed from inflexible material such as nylon or Teflon.

Buccal perfusion cells of the types mentioned above offer fixed (known) interfacial areas over which transfer can take place into a defined oral cavity membrane. The isolation of the area over which transfer occurs prevents interference from salivary secretions; thus aqueous phase volume, pH and temperature of the perfusant remain constant throughout the duration of experiment.

Human techniques: Animal models play an important role in the development of an oral mucosal drug delivery system, but these models are only appropriate to use for the screening of a series of compounds, investigating the mechanisms and usefulness of permeation enhancers or evaluating a set of formulations, if one is certain that the route of penetration, the structure and the composition of permeation barrier for both the drug and excipients are an exact mimic of its human counterpart.[27]

Until a suitable animal model is found whose absorption characteristics correlate well with its human counterpart and in which the route of penetration, structure and composition of the permeation barrier are considered, an exact mimic of human oral mucosa, the continued refinement of human methodologies is of utmost importance. Accurate measurement of the oral mucosal absorption characteristics of drugs in man is needed for the rational design of a delivery system.

Buccal absorption test: One of the simplest and direct measurement of penetration through the oral mucosa is the "Buccal Absorption Test". It was introduced by Beckett and Trigs in 1967. The test is simple, non-invasive method for estimating the rate and extent of drug disappearance from the oral cavity. The method involves controlled swirling of a buffered drug solution of known concentration around the oral cavity for a fixed time and then expelling it out. The difference between the amount of drug contained in the original solution and the amount recovered is assumed to be the amount of drug lost into the oral mucosa during the test period.[28]

Cell culture methods: *In vitro* cell culture models involving monolayer of cells of epithelial origin and grown on permeable support membranes have been increasingly used to study trans-epithelial drug transport and metabolism. *In vitro* cultures of cell have many advantages over conventional techniques including, a) rapid assessment if the potential permeability, b) the opportunity to elucidate the molecular mechanisms

of the drug transport, c) expanding limited human or animal tissue samples, d) the possibility if establishing a cell line which would provide a consistent, continuous supply of tissue, e) the ability to readily manipulate experimental conditions, f) the accessibility of both mucosal and serosal surface of tissue, and g) the opportunity to minimize time consuming, expensive and sometimes controversial animal studies.

There remains a challenge in the defining the conditions for the establishment of a culture system that completely mimics the complex *in vivo* tissue with respect to cell growth and differentiation, permeability and metabolism[29]

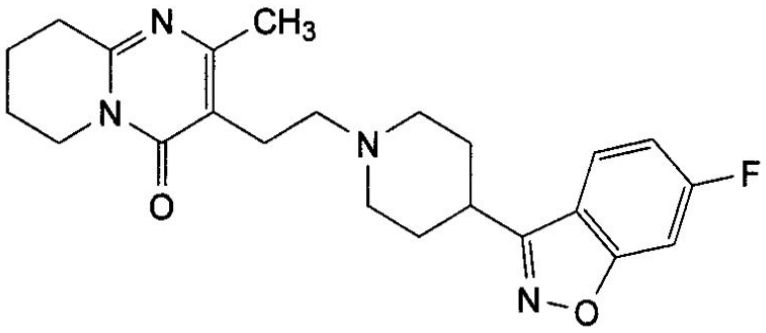
***In Vivo* Patch Test**

In this studied the release of drug from medicated buccal patches of benzydamine and lidocaine using human volunteers. The patches were applied to the upper gums of healthy volunteers and patches were removed at a particular time and dissolved in appropriate solvent/buffer and analysed spectrophotometrically.

DRUG PROFILE

RISPERIDONE

Structure:



Chemical Name: 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one

Empirical Formula: $C_{23}H_{27}FN_4O_2$

Molecular Weight: 410.49

Melting Point: 170 ^{o}C

Category: Antipsychotic[5]

Oral Dose: Initially 500 micrograms in two divided doses slowly increased in steps of 500 micrograms twice daily, generally at intervals of not less than 1 week and the maximum dose of risperidone is 10 mg/day in divided doses.[6]

Description: Solid, white to slightly beige powder.[30]

Solubility: Soluble in water and ethanol.

Log P (octanol/water): 3.49[5]

Storage: Risperidone should be stored at controlled room temperature 15 ^{o} – 25 ^{o}C (59^{o}-77 ^{o}F). Protect from light and moisture.

Pharmacokinetics[14]

Absorption: Risperidone is well absorbed orally. The absolute oral bioavailability of risperidone is 70%. Food does not affect either the rate or extent of absorption of risperidone. Thus, risperidone can be given with or without meals.

Distribution: Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. In plasma, risperidone is bound to albumin and α_1-acid glycoprotein. The plasma protein binding of risperidone is 90%, and that of its major metabolite, 9-hydroxyrisperidone is 77%. Neither risperidone nor 9-hydroxyrisperidone displaces each other from plasma binding sites. High therapeutic concentrations of sulfamethazine (100 mcg/ml), warfarin (10 mcg/ml), and carbamazepine (10mcg/ml) caused only a slight increase in the free fraction of risperidone at 10 ng/ml and 9-hydroxyrisperidone at 50 ng/ml, changes of unknown clinical significance.[31]

Metabolism and elimination: Risperidone is extensively metabolized in the liver. The main metabolic pathway is through hydroxylation of risperidone to 9-hydroxyrisperidone by the enzyme, CYP 2D6. A minor metabolic pathway is through *N*-dealkylation. The main metabolite, 9-hydroxyrisperidone, has similar

pharmacological activity as risperidone. Consequently, the clinical effect of the drug (i.e., the active moiety) results from the combined concentrations of risperidone plus 9-hydroxyrisperidone. CYP 2D6, also called debrisoquin hydroxylase, is the enzyme responsible for metabolism of many neuroleptics, antidepressants, antiarrhythmics, and other drugs. CYP 2D6 is subject to genetic polymorphism (about 6-8% of Caucasians, and a very low percentage of Asians, have little or no activity and are "poor metabolizers") and to inhibition by a variety of substrates and some non-substrates, notably quinidine. Extensive CYP 2D6 metabolizers convert risperidone rapidly into 9-hydroxyrisperidone, whereas poor CYP 2D6 metabolizers convert it much more slowly. Although extensive metabolizers have lower risperidone and higher 9-hydroxyrisperidone concentrations than poor metabolizers, the pharmacokinetics of the active moiety, after single and multiple doses, are similar in extensive and poor metabolizers.

Excretion: Risperidone and its metabolites are eliminated via the urine and, to a much lesser extent, via the feces. The apparent half-life of risperidone is 3 hours.

Pharmacodynamics

Mechanism of action: The mechanism of action of risperidone, as with other drugs used to treat schizophrenia, is unknown. However, it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5HT2) receptor antagonisms. Antagonism at receptors other than D2 and 5HT2 may explain some of the other effects of risperidone.

Risperidone is a selective monoaminergic antagonist with high affinity (Ki of 0.12 to 7.3 nM) for the serotonin Type 2 (5HT2), dopamine type 2 (D2), α1 and α2 adrenergic, and H1 histaminergic receptors. Risperidone acts as an antagonist at other

receptors, but with lower potency. Risperidone has low to moderate affinity (Ki of 47 to 253 nM) for the serotonin 5HT1C, 5HT1D, and 5HT1A receptors, weak affinity (Ki of 620 to 800 nM) for the dopamine D1 and haloperidol-sensitive sigma site, and no affinity (when tested at concentrations >10-5 M) for cholinergic muscarinic or β1 and β2 adrenergic receptors.

Indications: Risperidone is mainly indicated for the treatment of schizophrenia and other psychoses and also in the short-term treatment of mania associated with bipolar disorder.

Contraindications: Risperidone is contraindicated in patients with a known hypersensitivity to it.[31]

Adverse Effects: Risperidone is reported to be less likely to cause sedation or extrapyramidal effects but agitation may occur more frequently. Other common adverse effects include insomnia, anxiety, and headache. Dyspepsia, nausea and vomiting, abdominal pain, constipation, blurred vision, sexual dysfunction including priapism, urinary incontinence, rash and other allergic reactions, drowsiness, concentration difficulties, dizziness, fatigue, and rhinitis have been reported less commonly. In addition to orthostatic hypotension, hypertension has been reported infrequently. Other adverse effects with risperidone include cerebrovascular accidents, tachycardia, weight gain, oedema, increased liver enzyme values, and decreases in neutrophil or thrombocyte counts. Risperidone may cause dose-dependent increases in prolactin levels. In rare cases, hyperglycaemia and exacerbation of pre-existing diabetes mellitus have also been reported. Clinical monitoring for hyperglycaemia has been recommended, especially in patients with or at risk of developing diabetes. Other rare effects include seizures, body temperature

dysregulation, hyponatraemia, neuroleptic malignant syndrome, and tardive dyskinesia.

Risperidone should be used with caution in patients with cardiovascular disease, including conditions associated with QT prolongation, or conditions predisposing to hypotension. Caution is also recommended in patients with a history of or at risk of developing cerebrovascular disease, in patients with Parkinson's disease or epilepsy, and in patients with hepatic or renal impairment. Risperidone may affect the performance of skilled tasks such as driving.

Gradual withdrawal of risperidone is recommended because of the risk of withdrawal symptoms, including sweating, nausea and vomiting, and rebound psychosis, with abrupt cessation.

POLYMERS

Hydroxy Propyl Methyl Cellulose (HPMC 15, 47 cps) :

Hypromellose[32]

Description: It is an odorless and tasteless white or creamy-white colored fibrous or granular powder.

Functional category: Film former suspending agent, viscosity enhancer, tablet binding agent, coating agent, and emulsion stabilizer.

Solubility: Soluble in cold water, practically insoluble in chloroform and ether, but soluble in mixtures of methanol and dichloromethane.[33]

Stability and Storage conditions: Stable in dry conditions, solutions are stable in pH 3.0-11.0. Hydroxypropyl methylcellulose powder should be stored in a well-closed container, in a cool, dry place.

Incompatibilities: It is incompatible at extreme pH conditions and with oxidizing materials.

Applications

Oral Products: It is primarily used as a tablet binder in film-coating and as an extended release tablet matrix. Depending upon the viscosity grade, concentration between 2-10% w/w are used as film forming solutions to film-coat tablets. Lower viscosity grades are used in aqueous film-coating solution to film-coat tablets.

Topical products: It is used as a suspending and thickening agent in topical formulation, particularly ophthalmic preparations. It is also used as an emulsifier, suspending agent and stabilizing agent in topical gels and ointments. It is used as an adhesive in plastic bandages and as a wetting agent for hard contact lenses.

Ethylcellulose [32, 33]

Synonym: Ethylcellulosum

Functional category: Coating agent, tablet binder, viscosity-increasing agent.

Description: Ethylcellulose is a tasteless, free-flowing, white to light tan colored powder.

Solubility: Ethylcellulose practically insoluble in glycerin, propylene glycol and water. Ethylcellulose soluble in chloroform, methyl acetate, tetrahydrofuran, and in mixture of aromatic hydrocarbons with ethanol (95%).

Stability and storage conditions: Ethylcellulose is a stable, slightly, hygroscopic materials. It is chemically stable to alkalis, both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic materials than cellulose esters. The bulk materials should be stored in a dry place, in a well closed container at a temperature between 7-32 ºC.

Incompatibilities: Incompatible with paraffin wax and microcrystalline wax.

Application: Ethylcellulose is widely used in oral and topical pharmaceutical formulations. The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Ethylcellulose coatings are used to modify the release of drug. Ethylcellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films. Higher viscosity ethylcellulose grades are used to produce stronger and tougher films. In topical formulations, ethylcellulose is used as a thickening agent in creams, lotions or gels, provided an appropriate solvent is used. Ethylcellulose is additionally used in cosmetics and food products.

Poly Vinyl Pyrolidone (PVP): [34]

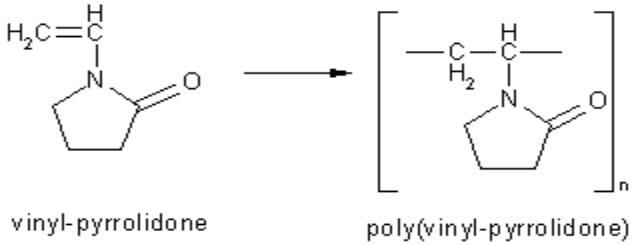
Functional category:

USP: Tablet binder, suspending and / or viscosity increasing agent

BP : Pharmaceutical excipient

Synonyms: Povidone; polyvinylpyrrolidone; PVP; kollidone; plasdone

Structure:



Empirical formula: $(C_6H_9NO)_n$

Molecular weight: 10, 000 - 700, 000

Description: A white to creamy white, odorless or almost odorless, hygroscopic powder.

Solubility: Readily soluble in water, organic solvents including monohydric (ethanol, methanol) and polyhydric alcohols, acids, esters, ketones, methylene chloride, chloroform, carbon tetra chloride.

Safety: Chemically, PVP is inert and nontoxic. It does not irritate the mucous membrane of rabbit eyes, is not antigenic and does not interfere in antibody formation studies.

Applications: Carrier for drug, Dispensing agent, Suspending or viscosity builder and Tablet binder, tablet diluents; Coating agent.

Based on the literature review, the necessary experiments were designed to prepare and evaluate the buccal films of risperidone. The details of materials and methods are given in the next chapter.

Methodology

METHODOLOGY

Drug

Risperidone	:	Micro Labs Ltd., Bangalore

Polymers

Polyvinyl pyrolidone	:	S.D. Fine Chemicals Ltd., Mumbai
Ethylcellulose	:	Ozone International, Mumbai
Hydroxypropyl methylcellulose (HPMC-15 cps)	:	Cadila Health Care Ltd., Ahmedabad
Hydroxypropyl methylcellulose (HPMC-47 cps)	:	Rolex Chemical Industries, Mumbai

Chemicals

Acetone	:	S.D. Fine Chem Ltd., Mumbai
Ethanol	:	Anilex Enterprises Inc., USA
Glycerin	:	Vikash Pharma, Goregaon., Mumbai
Hydrochloric acid	:	S.D. Fine Chem Ltd., Mumbai
Potassium dihydrogen phosphate	:	S.D. Fine Chem Ltd., Mumbai
Sodium hydroxide	:	S.D. Fine Chem Ltd., Mumbai
Tween 80	:	Loba Chemie, Mumbai

Instruments

Brookfield viscometer (LVDV-E)	:	Brookfield Engineering Labs. Inc., USA
Cyclone mixer	:	Remi Equipments, Bangalore
Digital balance	:	Shimadzu Corporation., Kyoto, Japan
Electronic single pan balance	:	The Oriental Balance Mfg. Co., Varanasi
FT / IR spectrometer 4100 (4000/6000 Series)	:	Jasco Corporation, Japan
Glass acrylic moulds	:	Fabricated locally
Magnetic stirrer	:	Remi Equipments, Bangalore
pH- meter	:	Control Dynamics, Bangalore
Digital thickness tester	:	Mitutoyo Corporation, Japan
Universal strength testing machine	:	Hounsfield., Slinfold, Horsham, U.K.
UV- Visible spectrophotometer (*UV*-1601 PC)	:	Shimadzu Corporation, Kyoto, Japan
Spirit level	:	K M B Suppliers, Bangalore
Water bath Bangalore	:	Research Test and Equipment,
Melting point apparatus	:	DBK Instruments, Mumbai
Dual Channel Potentiometer	:	Model – EQ 603

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Experimental Methods

Preparation of Buffers and Reagents

Phosphate buffer solution (pH 6.6): Dissolved 6.80 g of potassium dihydrogen orthophosphate (KH_2PO_4) and 0.656 gm sodium hydroxide in 1000 ml distilled water. The pH of the solution was adjusted to 6.6 using 0.5 N sodium hydroxide solution.

Hydrochloric acid solution (0.1 N): Concentrated hydrochloric acid solution (8.5 ml) was mixed with about 500 ml of distilled water in a 1000 ml volumetric flask. The volume was then made upto the mark with distilled water.

Analytical Methods

Preparation of Risperidone Standard Stock Solution (100 µg/ml) in 0.1N Hydrochloric Acid Solution

Standard stock solution of risperidone was prepared by dissolving accurately weighed 10 mg of risperidone in little quantity of methanol in 100 ml volumetric flask. The volume was then made up to 100 ml by using 0.1N hydrochloric acid solution to obtain the solution of 100 µg/ml.

Determination of Analytical Wavelength

Scanning of risperidone in 0.1N HCl solution by UV-spectrophotometry: From the standard stock solution, 1 ml was pippetted into a volumetric flask. The volume was then made upto 10 ml with 0.1 N hydrochloric acid solution. The resulting solution containing 10 µg/ml was scanned between 200 - 400 nm and the scan is shown in the Figure 04. The λ_{max} was found to be 270.6 nm, which was used as analytical wavelength.

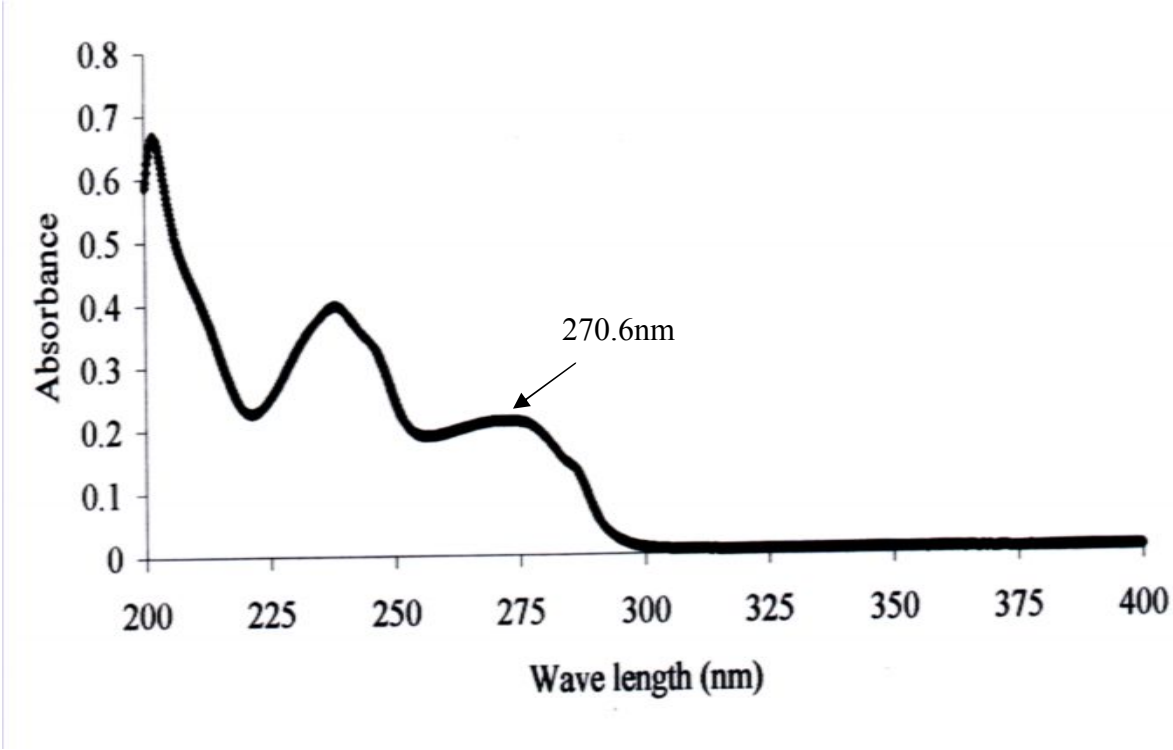


Figure 04: UV spectrum of risperidone in 0.1 N hydrochloric acid solution (10 µg/ml).

Calibration curve of risperidone in 0.1 N hydrochloric acid solution: From the risperidone standard stock solution (100 µg/ml), appropriate aliquots were taken into different volumetric flasks and made upto 10 ml with 0.1 N hydrochloric acid solution, so as to get drug concentrations of 0.0 to 40.0 µg/ml. The absorbencies of these drug solutions were estimated at λ_{max} 270.6 nm. This procedure was performed in triplicate to validate the calibration curve. The data including standard deviation (SD) values are given in the Table 03. A calibration curve was constructed as shown in the Figure 5. Regression value and equation for the calibration curve are also shown in the Figure 5.

Table 03

Data for calibration curve of risperidone in 0.1 N HCl solution at 270.6 nm

Sl. No.	Concentration (μg/ml)	Absorbance			AM ± SD
		Trial 1	Trial 2	Trial 3	
1	0.00	0.000	0.000	0.000	0.000 ± 0.0000
2	5.00	0.123	0.120	0.121	0.121 ± 0.0015
3	10.0	0.229	0.225	0.227	0.227 ± 0.0020
4	15.0	0.331	0.334	0.335	0.333 ± 0.0021
5	20.0	0.445	0.443	0.447	0.445 ± 0.0020
6	25.0	0.567	0.559	0.565	0.564 ± 0.0042
7	30.0	0.673	0.668	0.670	0.670 ± 0.0025
8	35.0	0.788	0.777	0.783	0.783 ± 0.0053
9	40.0	0.898	0.892	0.895	0.895 ± 0.0030

AM = Arithmetic mean; SD = Standard deviation

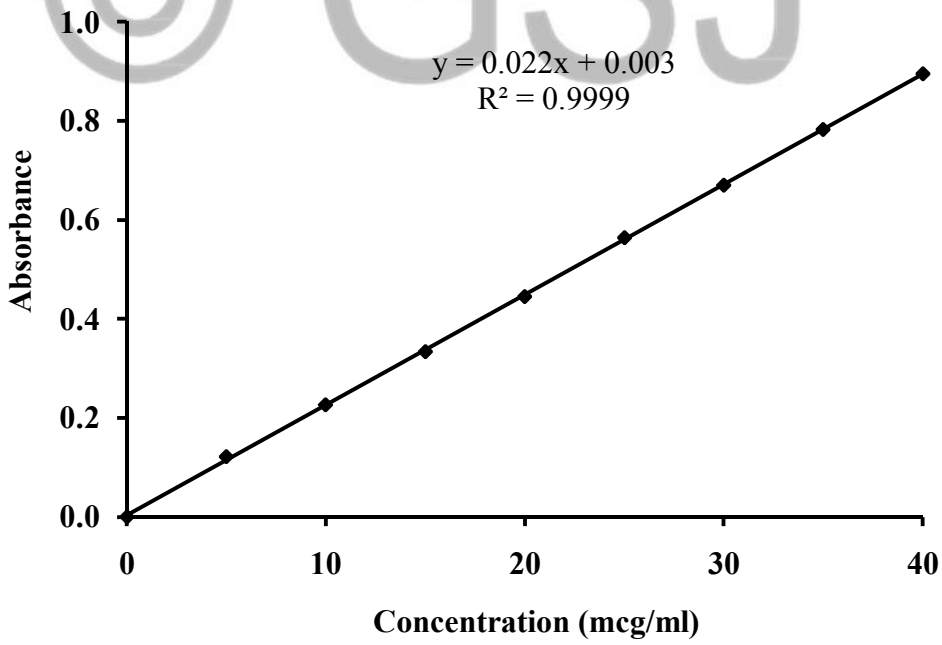


Figure 05: Calibration curve of risperidone in 0.1 N hydrochloric acid solution

Scanning of risperidone in phosphate buffer solution (pH 6.6) by UV – spectrophotometry : From the standard stock solution, 1 ml was diluted to 10 ml with phosphate buffer solution (pH 6.6). The resulting solution containing 10 µg/ml was scanned between 200 to 400 nm. The λ_{max} was found to be 277.2 nm.

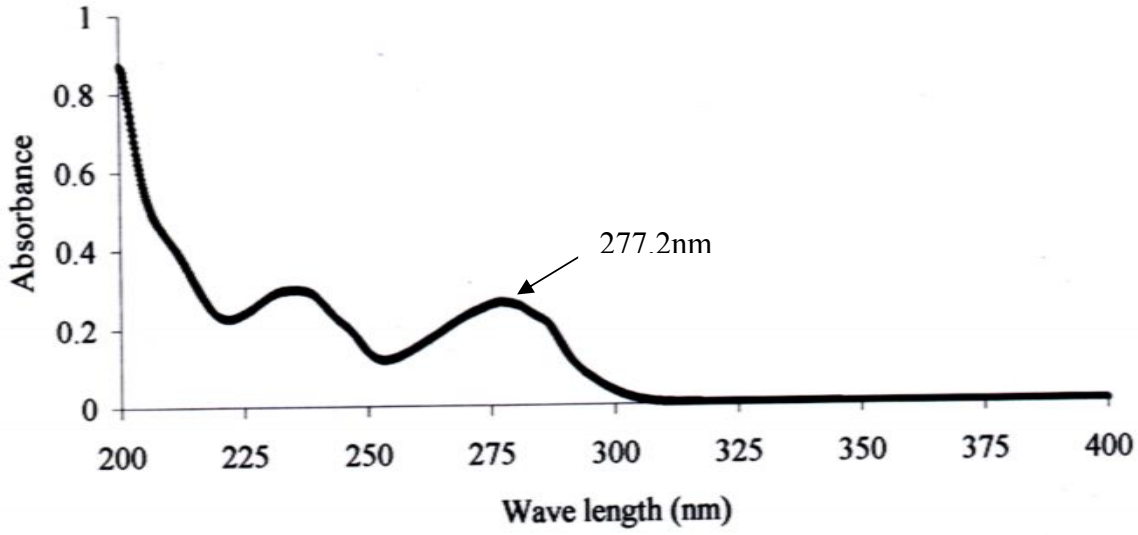


Figure 06: UV spectrum of risperidone (10 µg/ml) in phosphate buffer solution, pH 6.6.

Calibration curve of risperidone in phosphate buffer solution (pH 6.6): From the risperidone standard stock solution (100 µg/ml), appropriate aliquots were taken into different volumetric flasks and made up to 10 ml with phosphate buffer solution (pH 6.6), so as to get drug concentrations of 0.0 to 30.0 µg/ml. The absorbencies of these drug solutions were estimated at λ_{max} 277.2 nm. This procedure was performed in triplicate to validate the calibration curve. The data including standard deviation (SD) values are given in the Table 04. A calibration curve is constructed as shown in the Figure 06. Regression value and equation for the calibration curve are shown in the Figure 07.

Table 04

Data for calibration curve of risperidone in phosphate buffer solution (6.6 pH) at 277.2 nm

Sl. No.	Concentration (μg/ml)	Absorbance			AM ± SD
		Trial 1	Trial 2	Trial 3	
1	0.00	0.000	0.000	0.000	0.000 ± 0.0000
2	5.00	0.134	0.129	0.137	0.133 ± 0.0040
3	10.0	0.267	0.264	0.264	0.265 ± 0.0016
4	15.0	0.399	0.395	0.398	0.397 ± 0.0021
5	20.0	0.537	0.529	0.534	0.533 ± 0.0040
6	25.0	0.675	0.668	0.674	0.672 ± 0.0038
7	30.0	0.810	0.806	0.809	0.808 ± 0.0021

AM = Arithmetic mean; SD = Standard deviation

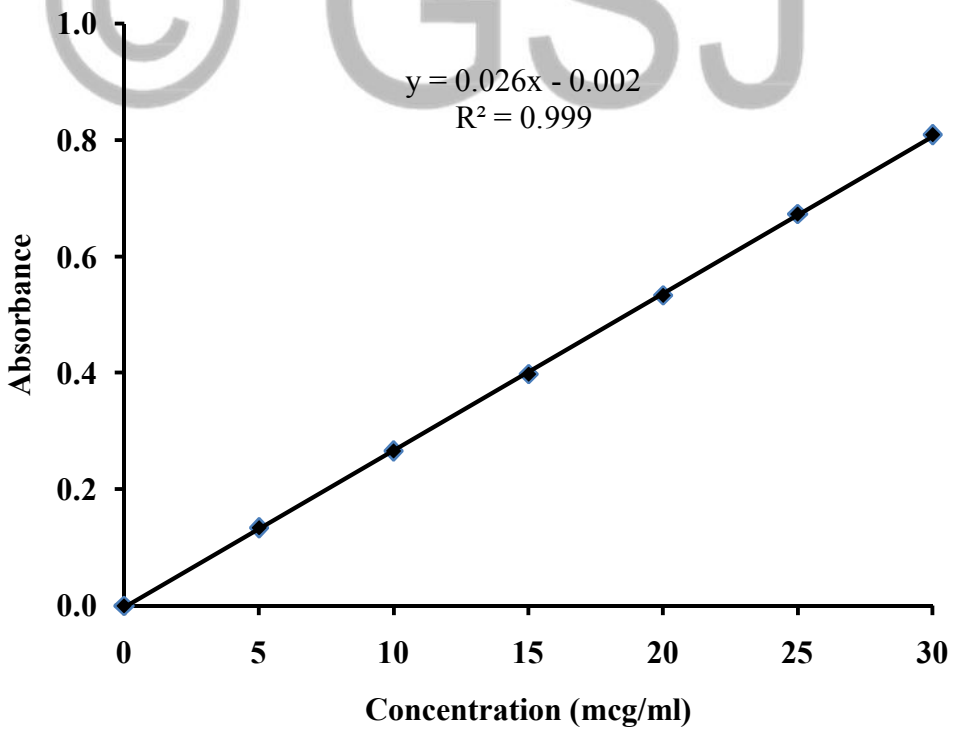


Figure 07: Calibration curve of risperidone in phosphate buffer solution, pH 6.6

Preformulation Studies

Interference of Polymers in the Estimations

Scanning of polymer solutions in 0.1 N hydrochloric acid solution: It is necessary to identify the incompatibility of polymer and drug for the analysis. Keeping in view of the concentration of polymer, an empirical concentration was fixed for the study of analysis. Solutions of polymers were prepared as per the concentrations given in the Table 05 using 0.1 N hydrochloric acid solution. The solutions were scanned in UV region i.e., 200-400 nm, using corresponding blank solutions. The Figures 08 - 11 represent the UV scans of polymeric solutions in hydrochloric acid solutions.

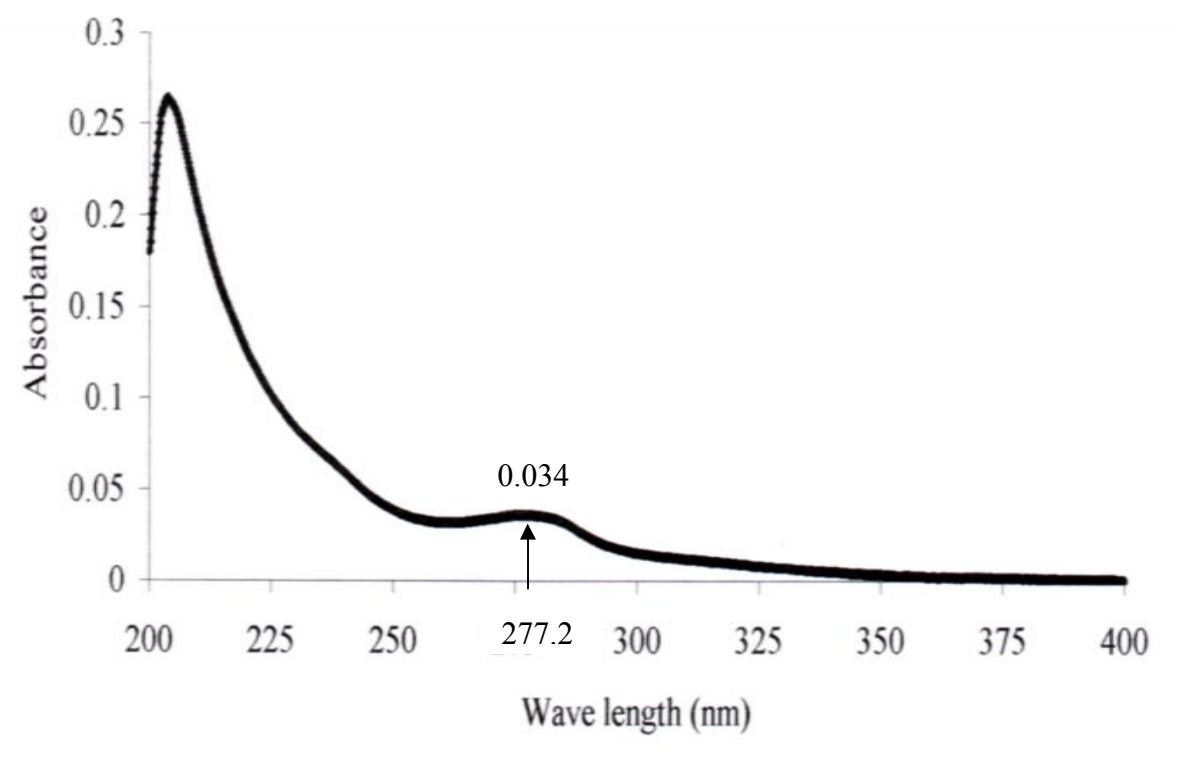


Figure 08: UV- spectrum of HPMC (15 cps) in 0.1N HCl solution (0.2% w/v)

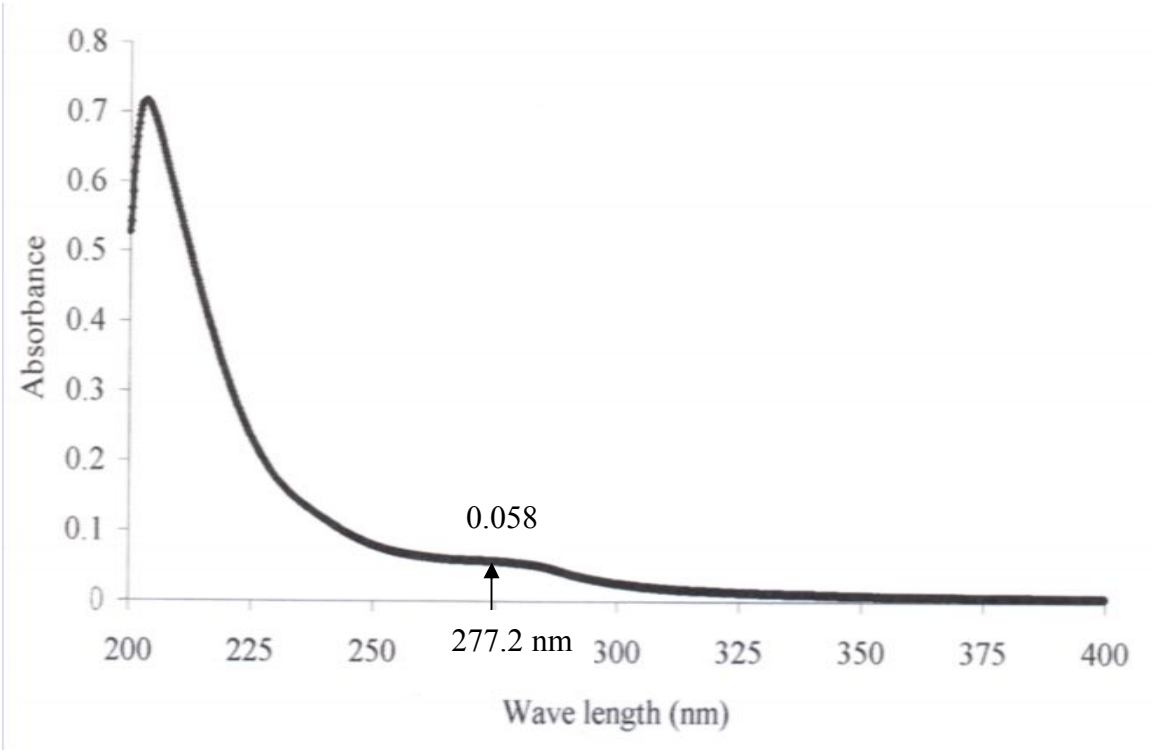


Figure 09: UV- spectrum of HPMC (47 cps) in 0.1N HCl solution (0.2% w/v)

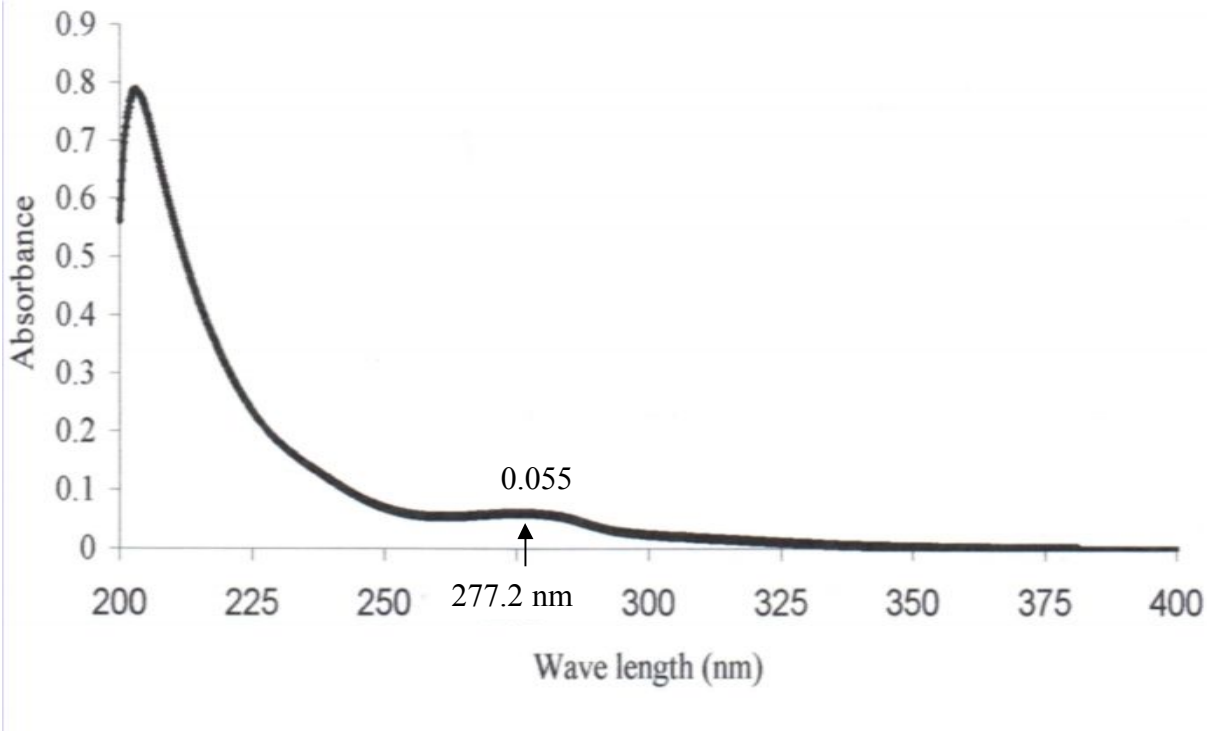


Figure 10: UV- spectrum of ethyl cellulose in 0.1 N HCl solution (0.1% w/v)

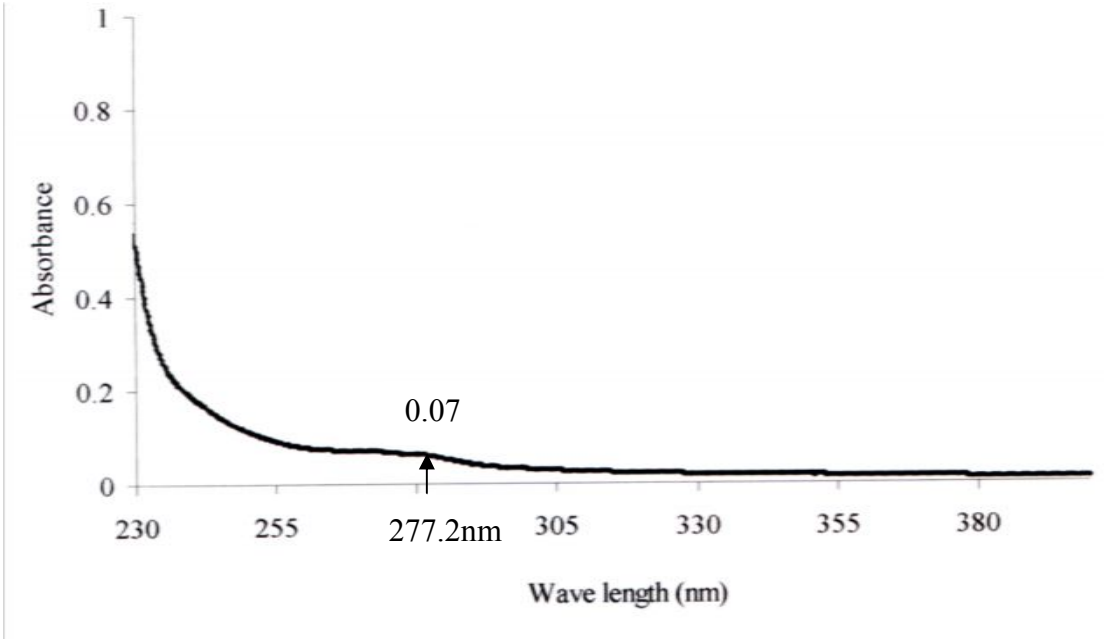


Figure 11: UV- spectrum of poly vinyl pyrrolidone in 0.1 N HCl solution (0.1% w/v)

Table 05: Data for estimation of interference of polymers

Polymer	Concentration (% w/v)	*Absorbance at 270.6 nm AM ± SD
HPMC 47 cps	0.2	0.038 ± 0.0040
HPMC 15 cps	0.2	0.054 ± 0.0037
Ethyl cellulose	0.1	0.377 ± 0.0030
PVP	0.1	0.074 ± 0.0046

*Each value is an average of three determinations, solvent used is 0.1 N hydrochloric acid solution, AM = Arithmetic mean, SD = Standard deviation

Fourier Transform Infrared Spectroscopy

The pure drug (risperidone) and polymers were subjected to FT-IR studies alone and in combination.[35,36,37] Three mg quantities of pure drug/pure polymer/combination of drug-polymer were mixed with 97 mg quantities of potassium bromide. Thorough grinding in smooth mortar effected mixing. The

mixtures were then placed in the sample holder of the instrument. These were analyzed by FT-IR to study the interference of polymer for drug analysis. Spectra are shown in Figures 13 to 17.

Assay

The purity of dried risperidone should be 99.0 to 101.0% as per British Pharmacopoeia.[30] Accurately weighed 0.160 g of risperidone was dissolved in 70 ml of 1 volume of anhydrous acetic acid and 7 volumes of methyl ethyl ketone and titrated with 0.1 M perchloric acid. The end point was determined potentiometrically. 1 ml of 0.1 M perchloric acid is equivalent to 20.53 mg of C_{23} H_{27} FN_4O_2.

Loss on Drying

The loss on drying of risperidone was determined by taking 1.0 g of drug and dried in an oven at 100-105 ^{O}C for four hours. The B.P limit for the loss on drying of risperidone is not more than 0.5%.[30]

Determination of Melting Point

Risperidone was filled in the capillary tube whose one end was closed by melting. The capillary tube was placed in the electrical melting point apparatus. The temperature was slowly increased with simultaneous observation of the sample. The temperature at which the drug starts melting was recorded as melting point. This process was repeated two more times. The mean of three readings was recorded.

Partition Co-efficient

Distribution co-efficient of risperidone was determined in the mixture of *n*-butanol-phosphate buffer solution, pH 6.6 by using shake flask method.[38] Five ml of *n*-butanol was taken and the drug was added till saturation. Then it was filtered. Out of this, 3 ml of filtrate was taken and mixed with 2 ml of *n*-butanol and 15 ml of phosphate buffer solution, pH 6.6. It was kept in a shaker bath for 24 hours at 25 °C.

The aqueous and *n*-butanol layers were separated by using separating funnel. One ml of aqueous solution was taken and 9 ml of solvent was added. Further dilutions were made. One ml of *n*-butanol layer was taken and 9 ml of methanol was added. From this 1 ml was taken and 9 ml of solvent was added and made necessary dilutions. The drug content present in each layer was estimated using UV-visible spectrophotometer.

Formulation Development

Preparation of Buccal Mucoadhesive Films

The casting method was followed in this study for preparation of films. About 7 patches of different composition of polymers were prepared. The films were observed for dispersion of drug, flexibility, and glossy structure. Based on the above observations, six formulations were selected and used for further analysis. The formulae are given in the Table 06. The words "film" and "patch" are carefully used in this dissertation though literature used them synonymously. The "film" represents the one, which was prepared from the mould and was bigger in size (5 x 3 cm^2) and patch represents the one, which was obtained by cutting the film and was smaller in size (1 x 1 cm^2).

Preparation of risperidone films: Buccal mucoadhesive films were prepared using polymer or polymer blends along with the drug and a suitable solvent**.** HPMC 15 cps (250 mg for film I) was weighed accurately and added in 4 ml of ethanol. The contents in the beaker were stirred on magnetic stirrer for 15 min for swelling of polymer. Further 1 ml of ethanol was added to the above polymer solution and stirred the dispersion. Then 3 drops (0.0882 g) of glycerin was added to the polymer solution. Risperidone (15 mg) was weighed and dissolved in 3 ml of ethanol and 1 drop of Tween 80 in another beaker. The drug solution was added to the polymer dispersion. The whole mixture was mixed thoroughly with the help of a magnetic

stirrer. The glass mould of size 5 × 3 cm^2 was placed over a flat surface, which was ensured using spirit level. The drug-polymer mixture was poured into the glass mould. An inverted funnel was placed over the mould overnight for controlled evaporation of the solvent. The film was removed from the mould and packed in wax paper and stored in a desiccator. On similar lines all films were prepared. Similarly, dummy patches were prepared without adding drug.

Table 06:Composition of different mucoadhesive formulations containing risperidone

Contents**	Formulation					
	I	II	III	IV	V	VI
Risperidone	15	15	15	15	15	15
HPMC, 15cps	250	*	200	*	200	*
HPMC, 47cps	*	250	*	200	*	200
Ethyl cellulose	*	*	50	50	*	*
PVP	*	*	*	*	50	50
Glycerin (3drops)	88.2	88.2	88.2	88.2	88.2	88.2
Ethanol	8	8	8	8	8	8
Tween 80 (1drop)	10.5	10.5	10.5	10.5	10.5	10.5

* No ingredient was added;
**All the ingredients are in mg except ethanol which was taken in ml
HPMC = Hydroxypropyl methylcellulose ; PVP = Poly vinyl pyrrolidone.

Evaluation

Thickness Uniformity

The thickness of each film was measured using Digimatic Micrometer at six different positions of the film and the average was calculated.[39]

Swelling Studies

Weight and area increase due to swelling of 6 patches were studied.[40]

Weight increase due to swelling: A drug-loaded patch of 1 x 1 cm^2 was weighed on a pre-weighed cover slip. It was kept into a petridish and 50 ml of phosphate buffer solution, pH 6.6 was added. After every five min, the cover slip was removed, wiped with tissue paper, and weighed again upto 30 min. The difference in the final and initial weight gives the weight increase due to absorption of water and swelling of patch.

Area increase due to swelling: A drug loaded patch of size of 1 x 1 cm^2 was cut and placed in a petridish. A graph paper was placed beneath the petridish, to measure the increase in the area. Fifty ml of phosphate buffer solution, pH 6.6, was poured into the petridish. An increase in the length and breadth of the patch was noted at five min intervals for 60 min and the area was calculated.

Tensile Strength and Percentage Elongation

Tensile strength and percentage elongation of the films was determined with Universal strength testing machine.[41] The sensitivity of the machine was 1 gram. It consists of two load cell grips. The lower one is fixed and upper one is movable (Figure 12). The test film of specific size (4 × 1 cm^2) was fixed between these cell grips and force was gradually applied till the film breaks. The tensile strength of the films was taken directly from the dial reading. The percentage elongation of the films was calculated by applying the following equations,

Percentage elongation = (Increase in length/ Original length) x 100

Figure 12: Universal strength testing machine

Percentage Moisture Loss

Percentage moisture loss was determined by keeping the patches (1 x 1 cm^2) in a desiccator containing anhydrous calcium chloride. After 3 days, the films were taken out, re-weighed and the percentage moisture loss was calculated using the following formula,

Percentage Moisture Loss = ((Initial weight – Final weight)/ Initial weight) x 100[39]

Uniformity of Weight of the Patches

Patches of size 1 x 1 cm^2 were cut. The weight of each patch was taken using Shimadzu (Shimadzu Corporation, Kyoto, Japan) balance with 0.0001 gram sensitivity and the weight variation of six patches was calculated. [39]

Surface pH

Buccal patches were left to swell for 1 hr on the surface of the agar plate, prepared by dissolving 2% w/v agar in warmed phosphate buffer solution, pH 6.6 under stirring and then poured the solution into the petridish till gelling/solidify at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen patch. The mean of three readings was recorded.[42]

Viscosity

Ethanolic solutions containing both polymer and plasticizer were prepared in the same concentration as that of patches. Brookefield viscometer (LVDV-E model) attached to the helipath spindle number 18 was used. The viscosity was measured at 60 rpm at room temperature. The recorded values were the mean of three determinations. [43]

Folding Endurance

The folding endurance of the patches was determined by repeatedly folding one patch at the same place till it broke or folded up to 300 times, which is considered satisfactory to reveal good film properties.[44] The number of times of film could be folded at the same place without breaking gave the value of the folding endurance. This test was done on all the patches for five times.

Drug Content Uniformity of Patches

The patches were tested for the content uniformity. A patch of size 1×1 cm^2 was cut and placed in a beaker.[45] Ten ml of 0.1 N hydrochloric acid solution was placed. The contents were stirred in cyclone mixer to dissolve the patch. The absorbance of the solution was measured using 0.1 N hydrochloric acid solution as blank at 270.6 nm.

In Vitro Release Studies

The patches containing risperidone were evaluated for *in vitro* release. The procedure followed is as given below.

A patch of 1 x 1 cm^2 size was cut and attached to a glass slide with a few drops of phosphate buffer solution (pH 6.6). This slide was kept at an angle of 45^o in a 250 ml beaker containing 100 ml of phosphate buffer solution (pH 6.6). The beaker was kept in circulating water bath in which the temperature was maintained at 37 ^oC. A non-agitated system was selected to eliminate any effect of turbulence on the release rate. Samples were withdrawn periodically after removing the slide from the beaker. The solution was stirred with a glass rod and 5 ml of sample was withdrawn using a graduated pipette, whose tip was attached to a tube with glass wool (as a filter). The slide was quickly reintroduced into the beaker. Five ml of the buffer was replaced immediately and the beaker was kept covered with a petridish to prevent evaporation of the fluid.[46] The samples were taken after every 5 min and analysed for drug content after necessary dilution with phosphate buffer solution, pH 6.6 at 277.2 nm. The release studies were conducted for three times and average was determined.

In Vivo Studies

***In vivo* patch test on rabbits:** *In vivo* absorption studies were conducted on rabbits for the best formulation out of six prepared.[40] Three male rabbits weighing 2.0 to 4.0 kg were used for the release study of the risperidone. The animals were fasted for overnight with *adlibitum* before the experiment was carried out. Prior permission to carry out this work was taken and the letter from the Institutional Ethics Committee is enclosed.

The rabbits were anesthetized with combination of phenobarbital sodium IP and ketamine hydrochloride (30 mg/kg) by *i.p.* route. Patches of size 1 x 1 cm^2 were cut

and fixed on a cellophane paper which acts as a backing layer so that the drug release was made unidirectional and thread was tied to it, so that the patches can be easily removed from the buccal cavity. After 10 min of the anaesthetic injection, the patches were placed (separately) in the buccal cavity one at a time. The patches were taken out at 10, 20, and 30 min (Patch V). The patches were dissolved in 10 ml of phosphate buffer solution, pH 6.6. The drug present in the patch represents drug remain unabsorbed which was analysed by measuring its absorbance at 277.2 nm using phosphate buffer solution, pH 6.6 as blank. The process was repeated three times to validate the results.

Buccal absorption test: Buccal absorption test was carried out on human volunteers as per the procedure described earlier with prior permission from Institutional Ethics Committee.[35] Since this test indicates the *prima facei* evidence of buccal absorption of risperidone, only three human volunteers were selected. Accurately weighed risperidone (10 mg) was dissolved in 10 ml of ethanol (1 mg/ml). From this solution, one ml was withdrawn and added 24 ml of phosphate buffer solution (6.6 pH). This solution was placed in the volunteer's mouth and with the movement of cheeks and tongue, the solution was circulated for about 300-400 times round the mouth for 5 min. Then solution was expelled. The volunteers were instructed to quickly rinse the mouth with buffer solution (10 ml) for 10 seconds and expelled the rinsing solution. The expelled solutions were combined and used for analysis after necessary dilution with phosphate buffer, pH 6.6. Corresponding blank solutions were simultaneously prepared. The drug content was analyzed at λ_{max} 277.2 nm.

***In vivo* patch test on human volunteers:** A patch of 1 x 1 cm^2 containing 1.0 mg of risperidone was cut and fixed on a cellophane paper, which acted as a backing layer so that the drug release was made unidirectional. [21] Before application

of the patch, the human volunteers were asked to rinse their mouth thoroughly with water. The patches were applied to the buccal mucosa of human volunteers for 10 min. After specified time (10 min), the patches were taken out and added to a beaker containing 10 ml of phosphate buffer solution (pH 6.6). The volunteers were directed to rinse their mouth with 10 ml of phosphate buffer solution (pH 6.6). The washing was added to the previous solution. After appropriate dilution with phosphate buffer, pH 6.6, solutions were analyzed for drug content at 277.2 nm. Second and third patches were applied for 20 and 30 min, respectively. Every time new patches were used. The results represent the amount of drug remaining unabsorbed. The approval letter from the Institutional Ethics Committee to carry out this work is enclosed.

Ageing[48]

Optimized medicated patches were subjected to short term stability testing. Patches were placed in a glass beaker lined with aluminium foil and maintained at $40 \pm 2\ ^{O}C$ and $75 \pm 5\%$ RH for 1 month as per ICH guidelines. Apart from this the patches were also exposed to room conditions for 1 month. Changes in the appearance and drug content of the stored patches were investigated after storage. The data presented are the mean of three determinations.

The results obtained in these methods and the discussion arrived from them are given in the following chapter “Results and Discussion”.

Results and Discussion

RESULTS AND DISCUSSION

The results and discussion are described under different headings as follows.

Analytical Methods

Calibration curves of risperidone in 0.1 N HCl solution and phosphate buffer (pH 6.6) solutions were plotted. This method was well validated and reproducible. Drug-Polymer interaction was not observed.

Preformulation Studies

The following preformulation studies were performed on risperidone and excipients.

Drug – excipient compatibility studies:[36,37] As described in the methodology section the FT-IR studies were carried out for pure drug alone and in combination with polymers. The results are summarized as follows. An FT-IR spectrum of pure risperidone is shown in the Figure 13 and peaks are listed in the Table 07. Similarly FT-IR spectra of risperidone in combination with polymers are shown in Figures 14 to 17. The peaks given in the Table 07 can be characteristic peaks of risperidone. These peaks were not affected and prominently considered as observed in FT-IR spectra given in Figures 13 to 17. This indicates that there is no interaction between risperidone and polymers and the drug was compatible with the formulation components.

Table 07: Data of the FT-IR spectra of pure risperidone and polymers

Ingredients	Peaks of functional groups (cm^{-1})						
	CH-stretching (Aromatic)	CH-stretching (Aliphatic)	C=C Stretching	C=N stretching	C–H bending (Aliphatic)	C–N stretching	C–F stretching
Risperidone	3069.16	2946.70	1536.02	1449.24	1414.53	1350.89	1132.01
Risperidone + HPMC 15	3067.16	2946.70	1536.99	1449.24	1414.53	1350.89	1131.05
Risperidone + HPMC 47	3067.23	2947.66	1536.02	1449.24	1413.53	1351.86	1132.01
Risperidone +Ethyl cellulose	3069.16	2947.66	1536.02	1472.38	1415.49	1350.89	1130.08
Risperidone + PVP	3066.26	2947.66	1536.02	1449.24	1414.53	1351.86	1132.01

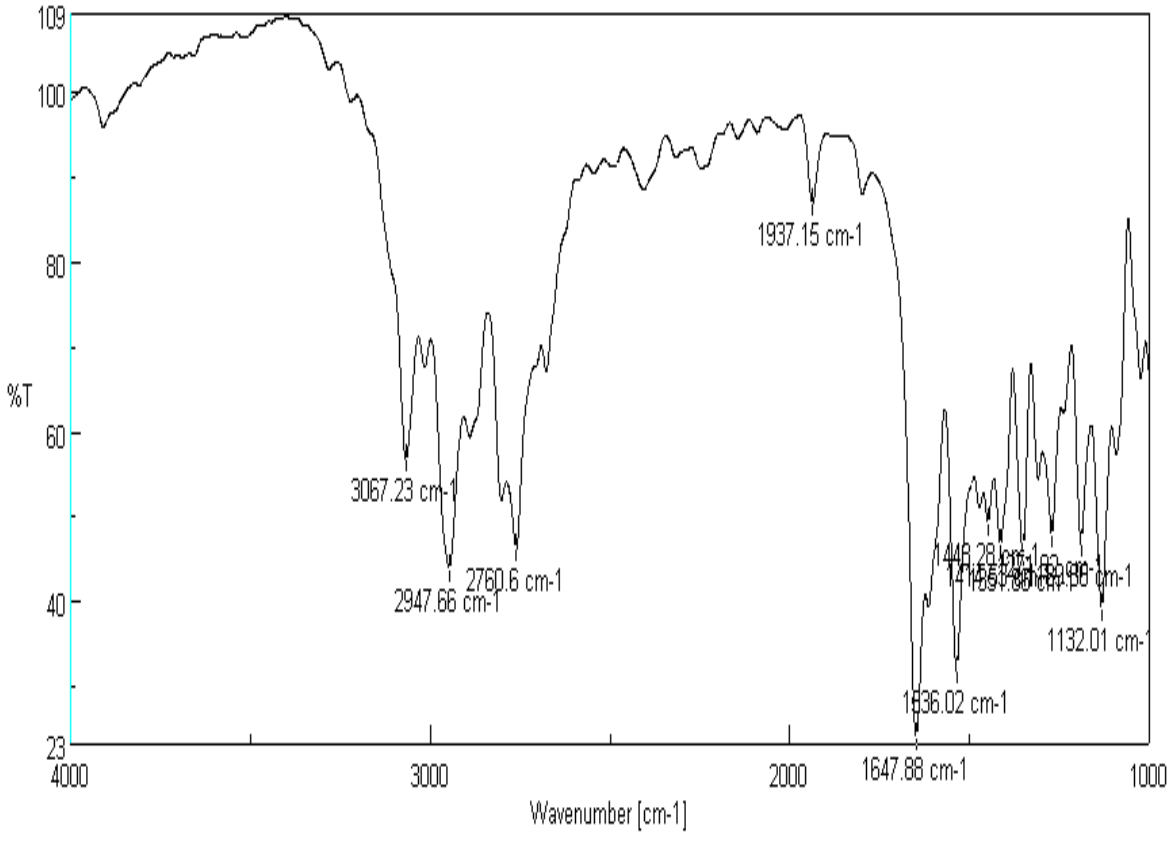


Figure 13: FT-IR spectrum of pure risperidone

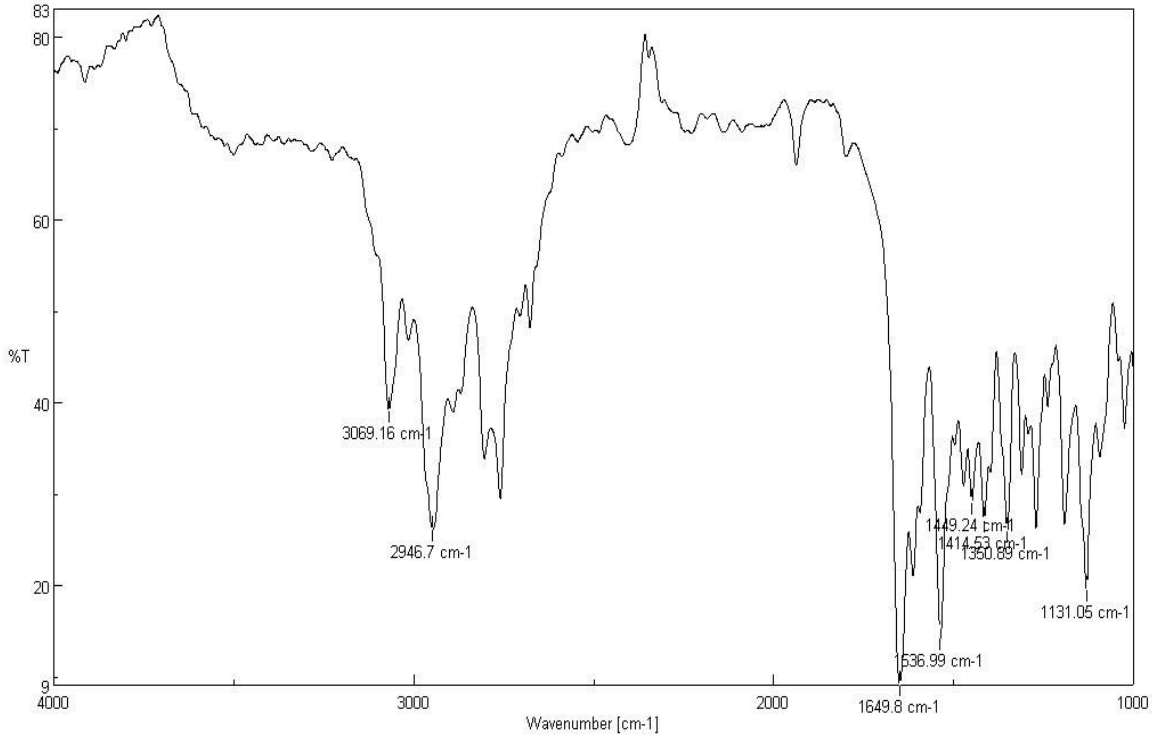


Figure 14: FT-IR spectrum of pure risperidone and HPMC 15 cps mixture

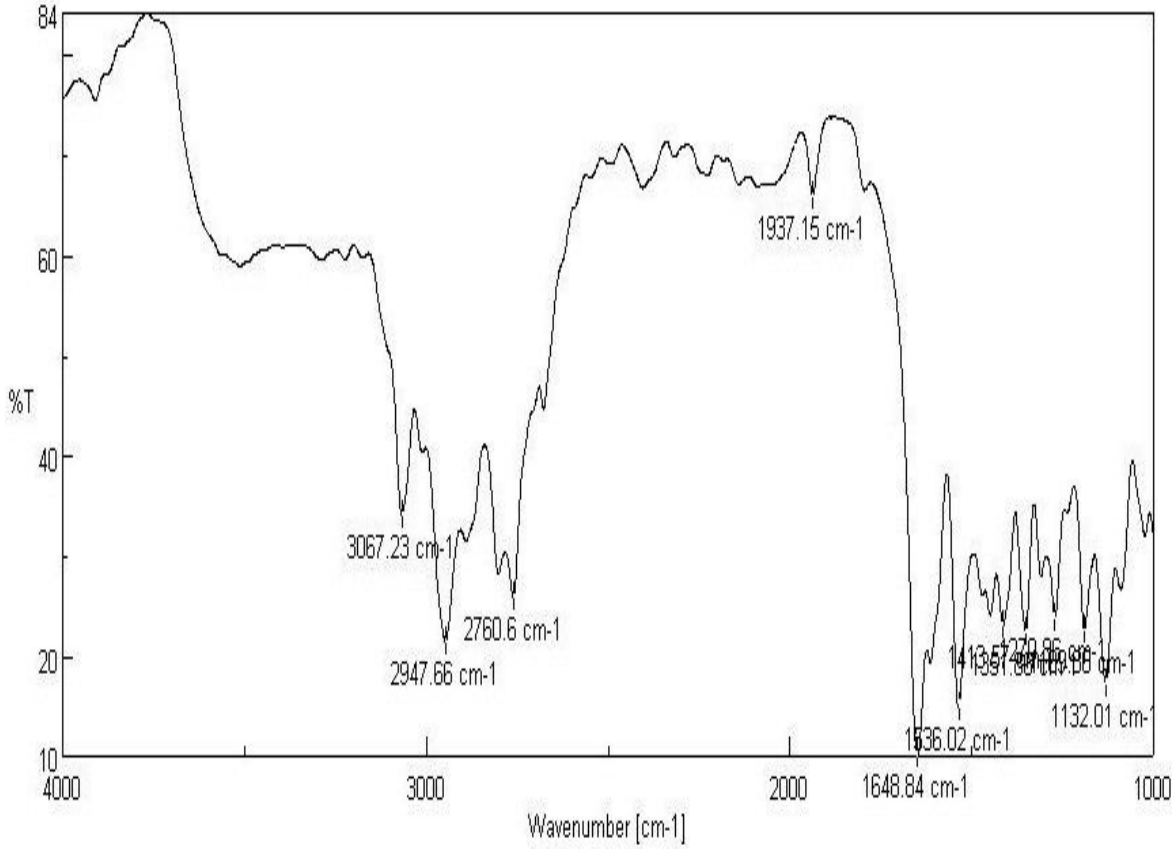


Figure 15: FT-IR spectrum of pure risperidone and HPMC 47 cps mixture

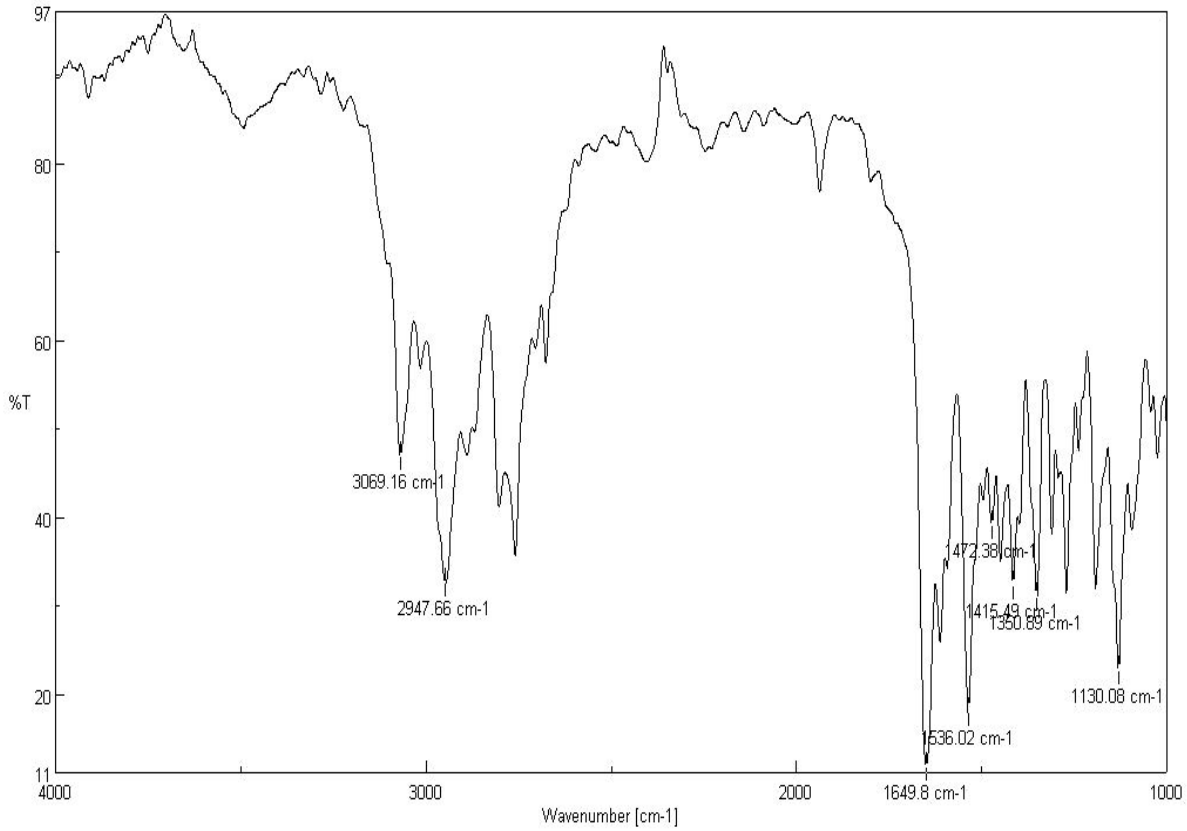


Figure 16: FT-IR spectrum of pure risperidone and ethyl cellulose mixture

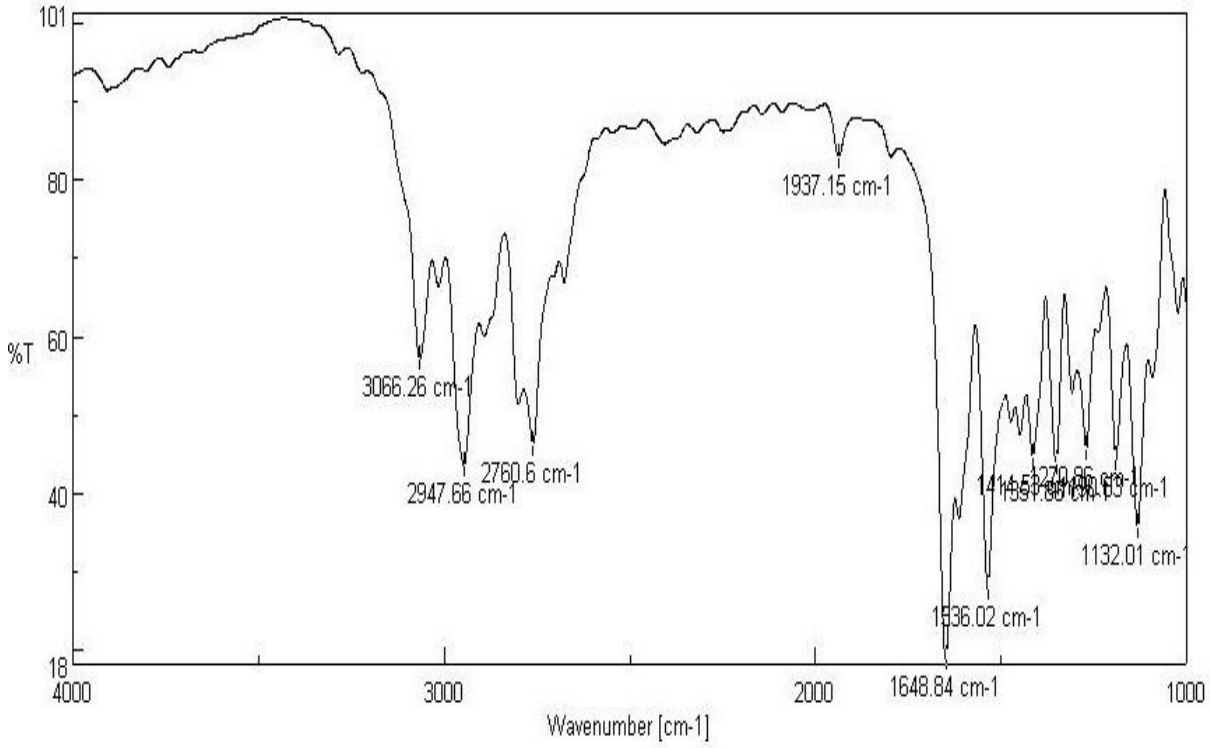


Figure 17: FT-IR spectrum of pure risperidone and PVP mixture

Assay: The assay of risperidone was determined by potentiometric method. The % purity of risperidone was found to be 100.89 and was within the limits of ± 1% as described in B.P.[30]

Loss on drying: The loss on drying of risperidone was 0.0533% which was within the limit of 0.5% as described in B.P.[30]

Dissociation constant: Risperidone reported value of literature for p*K*a is 7.89. This is considerably suitable for buccal administration.

Partition coefficient: Risperidone is rapidly and extensively absorbed after oral administration. However log *P* of risperidone determined in *n*-butanol-phosphate buffer solution (pH 6.6) was 2.1015 ± 0.1641. This value satisfied the requirement for buccal absorption and the subsequent buccal absorption test had supported the evidence.

Melting point: Melting point of risperidone determined by open capillary tube method was 169.6667 ± 0.5774 ^{o}C (*n* = 3). This value is same as that of the literature citation of 170 ^{o}C.[30]

Buccal absorption test: Buccal absorption test was proposed for some basic and acidic drugs. It was suggested as an *in vivo* model for passive drug transfer through lipid membrane.

From the above reports, the following aspects were considered

i) Absorption of drugs increases linearly with the time of contact of the drug solution with buccal membrane. It was found that a rapid absorption of drug takes place upto 5 min. In this study, the contact time was fixed at 5 min for buccal absorption test.

ii) Keeping in view of the dose of risperidone (i.e., 1-10 mg), a 1.0 mg dose was fixed in the study.

iii) Though the pH of the saliva ranges from 5.8 - 7.0, many researchers carried out buccal absorption test at pH 6.6. Therefore, pH 6.6 was selected in the present study.

The test was conducted on human volunteers and the data are given in the Table 08. Since this test indicates the *prima facei* evidence of buccal absorption of risperidone, only three human volunteers were selected. The phosphate buffer solution, pH 6.6, without drug was also conducted. This solution was used as a blank for the estimation of drug.

Table 08: Human buccal absorption test for risperidone

Volunteer code	Amount of drug unabsorbed (mg)	% Amount drug unabsorbed after 5 min	% Amount drug absorbed
HV_1	0.6422	64.22	35.78
HV_2	0.8208	82.08	17.92
HV_3	0.7538	75.38	24.62

*Amount of risperidone used was 1.0 mg in 25 ml of the buffer, pH 6.6
Time of contact = 5 min;
HV= Human Volunteer;
AM $\pm$ SD of drug absorbed = 26.10 $\pm$ 9.0231

From the results, it was observed that the percentage of drug absorption ranged from 17.92 to 35.8. The average percent amount of drug absorbed was 26.10 $\pm$ 9.023.

These results were encouraging. Absorption of drugs is dependent on the concentration gradient and therefore, it may be possible to increase the amount of absorption by increasing the dose of the drug administered. Higher absorption could be possible, with the increased contact time. The present model is a dynamic model,

excessive movements of swirling also impede the absorption of the drug to a certain extent. These results encouraged the designing of buccal adhesive patches of risperidone.

Formulation

Buccal Mucoadhesive Films of Risperidone

Risperidone films in polymers were prepared by casting method. The films of HPMC (47 and 15 cps) were prepared. HPMC films were also prepared using different copolymers like ethyl cellulose and polyvinyl pyrolidone. Plasticizer such as glycerin was used to get a film of good strength and less brittleness. Formulated patches were subjected to the preliminary evaluation tests. Patches with any imperfections, entrapped air, or differing in thickness, weight (or) content uniformity were excluded from further studies.

Evaluation

Physical Characteristics of Patches

The patches were translucent, having good strength, and visually smooth surfaced. The drug and polymer distribution was uniform.

Thickness uniformity of films: All the drug-loaded films have uniform thickness throughout. Standard deviation of all the films ranged between 0.0026 and 0.0089.

Table09: Thickness determinations of risperidone films

Sl. no.	Patch code	Average thickness* (mm) AM ± SD
1	I	0.2018 ± 0.0026
2	II	0.1951 ± 0.0040
3	III	0.2125 ± 0.0053
4	IV	0.2272 ± 0.0074
5	V	0.1753 ± 0.0055
6	VI	0.1858 ± 0.0089

*Each reading is an average of six determinations

Uniformity of weight of patches: Drug loaded patches (1 x 1 cm^2) were tested for uniformity of weight and the results are given in the Table 10. All the patches were found uniform. Standard deviation of all the patches ranged between 0.2926 and 1.4167.

Table 10: Uniformity of weight of risperidone patches

Sl. no.	Patch code	Average weight, * (mg) AM ± SD
1	I	14.6833 ± 0.2926
2	II	16.2330 ± 0.3076
3	III	20.5000 ± 1.3236
4	IV	22.8500 ± 1.4167
5	V	19.4000 ± 1.3115
6	VI	22.8500 ± 1.1725

* Each reading was an average of five determinations

Swelling studies of the patches: The swelling of the drug loaded patches of size 1 x 1 cm^2 was studied upto 30 min in case of change in weight and 60 min in case of change in area. The swelling of the patches were observed in phosphate buffer solution (pH 6.6). The data for increase in weight due to swelling are given in the

Tables 11 to 16 for patches I to VI, respectively. The entire data are shown in the Figure 18. The order of % increase in weight is IV < III < II < VI < I < V. Swelling was more pronounced in patch V and I which contains HPMC (15 cps). Patches IV showed least swelling (weight basis), may be due to the presence of ethyl cellulose.

Table 11: Swelling studies of risperidone patch I - Change in weight

Sl. no.	Time (min)	Weight of patch I (mg) AM ± SD	Increase in weight (mg) AM ± SD	Percent increase in weight * AM ± SD
1	0	14.733 ± 0.1527	-	-
2	5	54.000 ± 0.7211	39.266 ± 0.6658	366.5260 ± 4.6640
3	10	80.600 ± 1.9467	65.866 ± 1.8929	547.0631 ± 12.2439
4	15	90.200 ± 0.4582	75.466 ± 0.3511	612.2442 ± 4.3612
5	20	103.430 ± 1.8248	88.700 ± 2.0297	702.0630 ± 14.1780
6	25	113.233 ± 1.5176	98.500 ± 1.6703	768.6770 ± 18.2130
7	30	118.000 ± 1.3527	104.066 ± 1.5011	806.4530 ± 17.3710

*Each reading is an average of three values

Table 12: Swelling studies of risperidone patch II-Change in weight

Sl. no.	Time (min)	Weight of patch II (mg) AM ± SD	Increase in weight (mg) AM ± SD	Percent increase in weight * AM ± SD
1	0	16.1667 ± 0.3055	-	-
2	5	69.7667 ± 5.7187	53.6000 ± 5.6027	324.84 ± 33.95
3	10	89.0667 ± 6.2132	72.9000 ± 6.0556	441.81 ± 36.70
4	15	105.700 ± 5.4745	89.5333 ± 5.2310	542.62 ± 31.70
5	20	118.5333 ± 8.4571	102.3667 ± 8.1868	620.40 ± 49.61
6	25	134.4667 ± 6.0666	118.3000 ± 5.8847	716.96 ± 35.66
7	30	145.6000 ± 7.5545	129.4333 ± 7.4702	784.44 ± 45.27

* Each reading is an average of three values.

Table 13: Swelling studies of risperidone patch III - Change in weight

Sl. no.	Time (min)	Weight of patch III (mg) AM ± SD	Increase in weight (mg) AM ± SD	Percent increase in weight * AM ± SD
1	0	18.5000 ± 0.8718	-	-
2	5	54.6333 ± 10.2919	36.1333 ± 11.0753	197.25 ± 66.75
3	10	71.0000 ± 9.4440	52.5000 ± 10.015	285.31 ± 63.17
4	15	74.4667 ± 11.2855	55.9667 ± 11.8154	304.18 ± 72.97
5	20	84.4333 ± 5.9919	65.9333 ± 6.5363	357.62 ± 47.35
6	25	97.0000 ± 8.8097	78.5000 ± 9.5911	426.37 ± 68.77
7	30	102.7333 ± 5.1791	84.2333 ± 5.6323	456.50 ± 45.47

* Each reading is an average of three values.

Table 14: Swelling studies of risperidone patch IV-Change in weight

Sl. no.	Time (min)	Weight of patch IV (mg) AM ± SD	Increase in weight (mg) AM ± SD	Percent increase in weight * AM ± SD
1	0	22.3000 ± 0.9849	-	-
2	5	49.8667 ± 9.9123	27.5667 ± 9.9289	147.5 ± 46.53
3	10	60.6667 ± 2.8210	38.3667 ± 8.8681	206.41 ± 39.15
4	15	66.3667 ± 6.4663	44.0667 ± 5.9248	237.57 ± 20.58
5	20	76.5000 ± 3.7470	54.2000 ± 2.7622	293.21 ± 15.99
6	25	84.2667 ± 5.3379	61.9667 ± 4.3662	335.29 ± 25.90
7	30	89.1000 ± 8.4640	66.8000 ± 7.4907	361.32 ± 41.2

* Each reading is an average of three values.

Table 15: Swelling studies of risperidone patch V-Change in weight

Sl. no.	Time (min)	Weight of patch V (mg) AM ± SD	Increase in weight (mg) AM ± SD	Percent increase in weight * AM ± SD
1	0	19.4000 ± 1.1533	-	-
2	5	89.4333 ± 14.1076	22.7 ± 3.244	364.96 ± 101.48
3	10	122.0667 ± 13.1668	42.266 ± 3.583	533.41 ± 106.90
4	15	142.4000 ± 12.0462	55.866 ± 1.289	637.55 ± 98.11
5	20	158.0333 ± 13.1093	70.3 ± 4.176	718.45 ± 107.26
6	25	174.9667 ± 5.0649	86.433 ± 6.213	805.02 ± 79.68
7	30	179.2666 ± 4.1621	93.666 ± 3.300	827.15 ± 78.13

* Each reading is an average of three values.

Table 16: Swelling studies of risperidone patch VI-Change in weight

Sl. no.	Time (min)	Weight of patch VI (mg) AM ± SD	Increase in weight (mg) AM ± SD	Percent increase in weight * AM ± SD
1	0	21.2333 ± 1.4572	-	-
2	5	95.8333 ± 6.5241	74.6000 ± 7.7544	353.90 ± 58.30
3	10	127.2333 ± 7.4097	106.0000 ± 6.5200	500.08 ± 32.37
4	15	143.6667 ± 7.2947	122.4333 ± 7.9651	579.43 ± 70.32
5	20	164.2000 ± 13.7706	142.9667 ± 14.3685	676.99 ± 101.92
6	25	179.2333 ± 13.1325	158.0000 ± 13.9524	748.41 ± 109.08
7	30	188.3333 ± 12.4597	167.1000 ± 13.3180	791.39 ± 109.71

* Each reading is an average of three values.

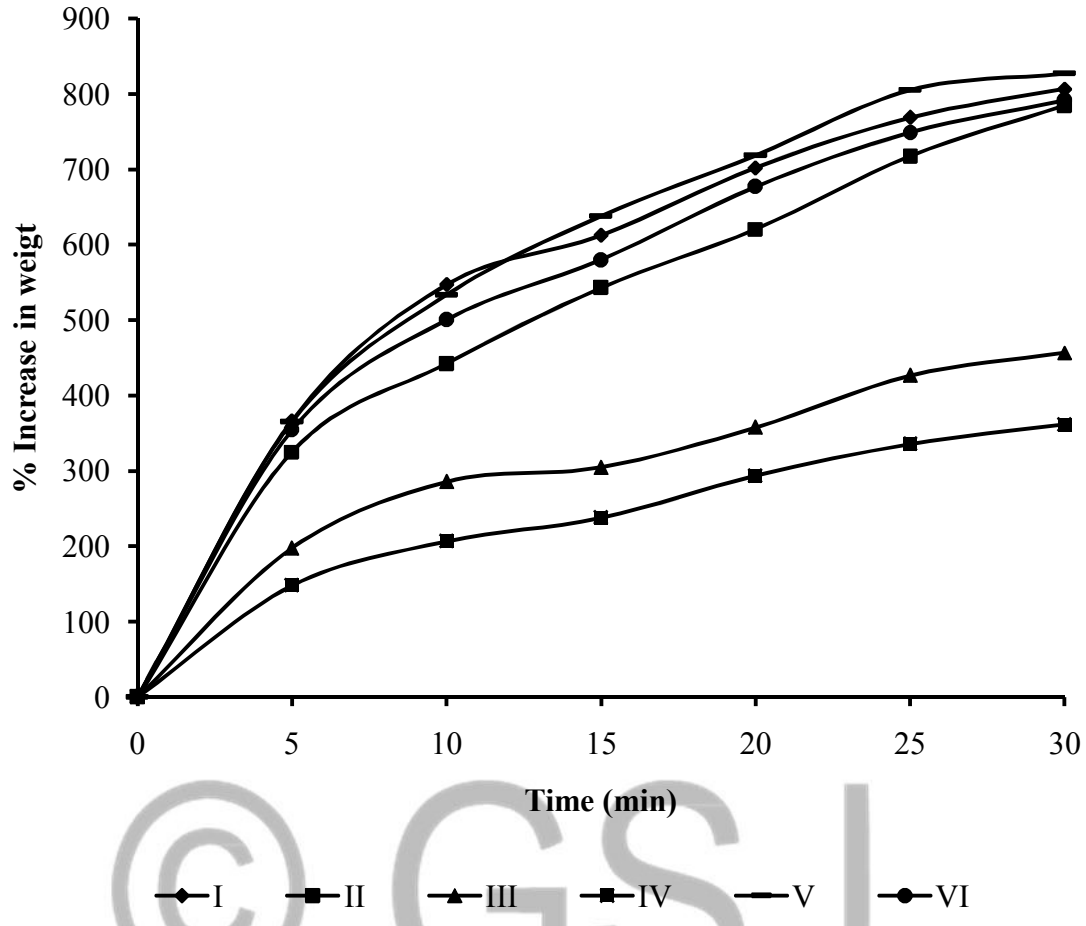


Figure 18: Swelling studies of risperidone patches - Change in weight in phosphate buffer in pH 6.6.

The data for the increase in area due to swelling are given in the Tables 15 to 22, respectively for patches I to V1. The data are shown in the Figure 19. The order of % increase in area is IV < III < II < I < VI < V. Swelling was more pronounced in patch V and VI which contain HPMC and PVP. These results were agreeing with the increase in weight due to swelling. Patch IV showed least increase in area due to swelling. This must be due to the ethyl cellulose.

Table 17: Swelling studies of risperidone patch I - Changes in area

Sl. no.	Time (min)	Area of patch I (cm^2) AM ± SD	Increase in area (cm^2) AM± SD	Percent increase in area* AM ± SD
1	0	1	-	-
2	5	1.0705 ± 0.0165	0.0705 ± 0.0165	7.0511 ± 1.6548
3	10	1.1140 ± 0.0135	0.1140 ± 0.0135	11.4040 ± 1.514
4	15	1.1630 ± 0.0202	0.1630 ± 0.0202	16.1972 ± 2.0236
5	20	1.2077 ± 0.0143	0.2077 ± 0.0143	20.7734 ± 1.4318
6	25	1.2394 ± 0.0142	0.2394 ± 0.0142	23.9417 ± 1.4223
7	30	1.2833 ± 0.0061	0.2833 ± 0.0061	28.3268 ± 0.6134
8	35	1.3594 ± 0.0273	0.3594 ± 0.0273	35.9378 ± 2.7336
9	40	1.4043 ± 0.0542	0.4043 ± 0.0542	40.4323 ± 5.4229
10	45	1.4510 ± 0.0584	0.4510 ± 0.0584	45.1032 ± 5.8386
11	50	1.4960 ± 0.0619	0.4960 ± 0.0619	49.5951 ± 6.1934
12	55	1.5383 ± 0.0643	0.5383 ± 0.0643	53.8307 ± 6.4281
13	60	1.5794 ± 0.0726	0.5794 ± 0.0726	57.9378 ± 7.2588

* Each reading is an average of three determinations.

Table 18: Swelling studies of risperidone patch II-Changes in area

Sl. no.	Time (min)	Area of patch II (cm^2) AM ± SD	Increase in area cm^2 AM ± SD	Percent increase in area* AM ± SD
1	0	1	-	-
2	5	1.0635 ± 0.0129	0.0635 ± 0.0129	6.35 ± 1.2891
3	10	1.0988 ± 0.0292	0.0988 ± 0.0292	9.88 ± 2.9200
4	15	1.1384 ± 0.0194	0.1384 ± 0.0194	13.84 ± 1.9441
5	20	1.1736 ± 0.0156	0.1736 ± 0.0156	17.36 ± 1.5606
6	25	1.2187 ± 0.0220	0.2187 ± 0.0220	21.87 ± 2.1989
7	30	1.2518 ± 0.0369	0.2518± 0.0369	25.18 ± 3.6866
8	35	1.2940 ± 0.0284	0.2940 ± 0.0284	29.40 ± 2.8438
9	40	1.3559 ± 0.0453	0.3559 ± 0.0453	35.59 ± 4.5335
10	45	1.4118 ± 0.0576	0.4118 ± 0.0576	41.18 ± 5.7576
11	50	1.4611 ± 0.0599	0.4611 ± 0.0599	46.11 ± 5.9904
12	55	1.5114 ± 0.0692	0.5114 ± 0.0692	51.14 ± 6.9197
13	60	1.5485 ± 0.0923	0.5485 ± 0.0923	54.88 ± 9.2349

* Each reading is an average of three determinations.

Table 19: Swelling studies of risperidone patch III - Changes in area

Sl. no.	Time (min)	Area of patch III (cm^2) AM ± SD	Increase in area cm^2 AM ± SD	Percent increase in area* AM ± SD
1	0	1	-	-
2	5	1.0458 ± 0.0083	0.0458 ± 0.0083	4.58 ± 0.8294
3	10	1.1077 ± 0.0455	0.1077 ± 0.0455	10.77 ± 4.5495
4	15	1.1290 ± 0.0229	0.1290 ± 0.0229	12.90 ± 2.2936
5	20	1.1691 ± 0.0135	0.1691 ± 0.0135	16.91 ± 1.3516
6	25	1.2095 ± 0.0146	0.2095 ± 0.0146	20.95 ± 1.4612
7	30	1.2622 ± 0.0195	0.2622 ± 0.0195	26.22 ± 1.9529
8	35	1.2969 ± 0.0101	0.2969 ± 0.0101	29.69 ± 1.0132
9	40	1.3448 ± 0.0073	0.3448 ± 0.0073	34.48 ± 0.7319
10	45	1.4034 ± 0.0075	0.4034 ± 0.0075	40.34 ± 0.7477
11	50	1.4469 ± 0.0141	0.4469 ± 0.0141	44.69 ± 1.4090
12	55	1.5020 ± 0.0288	0.5020 ± 0.0288	50.20 ± 2.8755
13	60	1.5289 ± 0.0293	0.5289 ± 0.0293	52.89 ± 2.9335

* Each reading is an average of three determinations.

Table 20: Swelling studies of risperidone patch IV - Changes in area

Sl. no.	Time (min)	Area of patch IV (cm^2) AM ± SD	Increase in area cm^2 AM ± SD	Percent increase in area* AM ± SD
1	0	1	-	-
2	5	1.0257 ± 0.0119	0.0257 ± 0.0119	2.5706 ± 1.1880
3	10	1.0588 ± 0.0275	0.0588 ± 0.0275	5.8766 ± 2.7496
4	15	1.0901 ± 0.0341	0.0901 ± 0.0341	9.0133 ± 3.4052
5	20	1.1285 ± 0.0359	0.1285 ± 0.0359	12.8545 ± 3.5931
6	25	1.1700 ± 0.0476	0.1700 ± 0.0476	16.9990 ± 4.7623
7	30	1.2029 ± 0.0487	0.2029 ± 0.0487	20.2894 ± 4.8697
8	35	1.2438 ± 0.0505	0.2438 ± 0.0505	24.3802 ± 5.0505
9	40	1.2707 ± 0.0530	0.2707 ± 0.0530	27.0690 ± 5.3040
10	45	1.3050 ± 0.0553	0.3050 ± 0.0553	30.4987 ± 5.5299
11	50	1.3578 ± 0.0528	0.3578 ± 0.0528	35.7813 ± 5.2782
12	55	1.3963 ± 0.0520	0.3963 ± 0.0520	39.6292 ± 5.2044
13	60	1.4272 ± 0.0506	0.4272 ± 0.0506	42.7204 ± 5.0580

*Each reading is an average of three determinations.

Table 21: Swelling studies of risperidone patch V - Changes in area

Sl. no.	Time (min)	Area of patch V (cm^2) AM ± SD	Increase in area cm^2 AM ± SD	Percent increase in area* AM ± SD
1	0	1	-	-
2	5	1.1069 ± 0.0076	0.1069 ± 0.0076	10.69 ± 0.7600
3	10	1.1424 ± 0.0352	0.1424 ± 0.0352	14.24 ± 3.5213
4	15	1.2016 ± 0.0337	0.2016 ± 0.0337	20.16 ± 3.3745
5	20	1.2436 ± 0.0314	0.2436 ± 0.0314	24.36 ± 3.1350
6	25	1.3012 ± 0.0396	0.3012 ± 0.0396	30.12 ± 3.9619
7	30	1.3491 ± 0.0293	0.3491 ± 0.0293	34.91 ± 2.9251
8	35	1.3795 ± 0.0275	0.3795 ± 0.0275	37.95 ± 2.7469
9	40	1.4388 ± 0.0281	0.4388 ± 0.0281	43.88 ± 2.8056
10	45	1.4867 ± 0.0286	0.4867 ± 0.0286	48.67 ± 2.8618
11	50	1.5321 ± 0.0300	0.5321 ± 0.0300	53.21 ± 3.0002
12	55	1.6106 ± 0.0466	0.6106 ± 0.0466	61.06 ± 4.6622
13	60	1.6494 ± 0.0648	0.6494 ± 0.6494	64.94 ± 6.4771

* Each reading is an average of three determinations.

Table 22: Swelling studies of risperidone patch VI - Changes in area

Sl. no.	Time (min)	Area of patch VI (cm^2) AM ± SD	Increase in area cm^2 AM ± SD	Percent increase in area * AM ± SD
1	0	1	-	-
2	5	1.1091 ± 0.0197	0.1091 ± 0.0197	10.91 ± 1.9746
3	10	1.1557 ± 0.0134	0.1557 ± 0.0134	15.57 ± 1.3438
4	15	1.2152 ± 0.0090	0.2152 ± 0.0090	21.52 ± 0.8959
5	20	1.2627 ± 0.0150	0.2627 ± 0.0150	26.27 ± 1.4956
6	25	1.2998 ± 0.0074	0.2998 ± 0.0074	29.98 ± 0.7422
7	30	1.3195 ± 0.0052	0.3195 ± 0.0052	31.95 ± 0.5181
8	35	1.3569 ± 0.0215	0.3569 ± 0.0215	35.69 ± 2.1489
9	40	1.3978 ± 0.0113	0.3978 ± 0.0113	39.78 ± 1.1299
10	45	1.4469 ± 0.0141	0.4469 ± 0.0141	44.69 ± 1.4090
11	50	1.4923 ± 0.0077	0.4923 ± 0.0077	49.23 ± 0.7717
12	55	1.5508 ± 0.0103	0.5508 ± 0.0103	55.08 ± 1.0313
13	60	1.5986 ± 0.0231	0.5986 ± 0.0231	59.86 ± 2.3074

* Each reading is an average of three determinations.

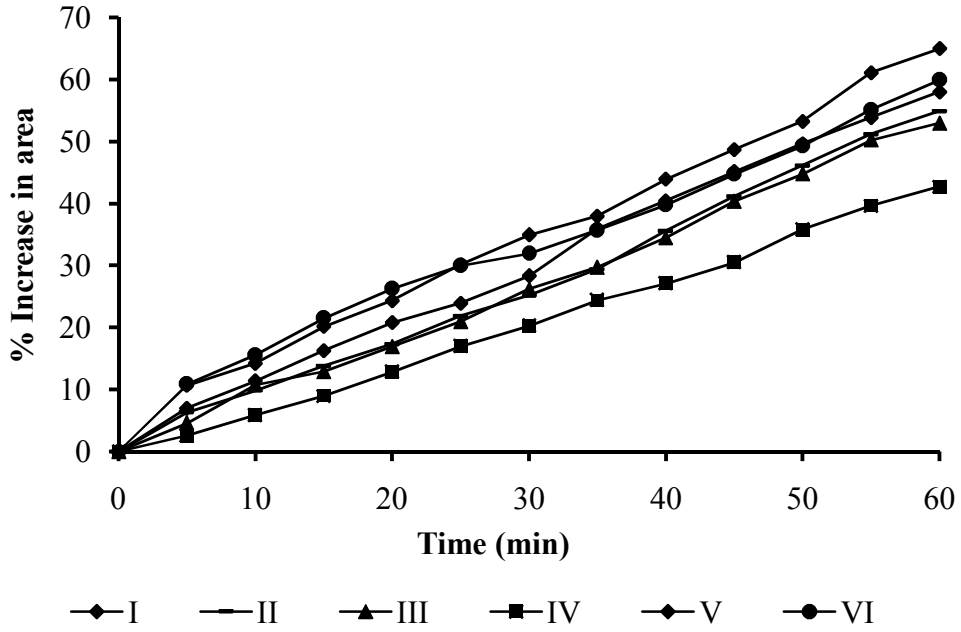


Figure 19: Swelling studies of risperidone patches - Change in area in phosphate buffer in pH 6.6

Tensile strength: Tensile strength was determined using Universal strength testing machine for the blank and drug loaded films. The data are given in the Table 23 and depicted in the Figure 21. The order of tensile strength of the film is IV >II >III >I >VI > V.

Table 23: Tensile strength of risperidone patches

Sl. no.	Patch Code		Tensile strength * (kg) AM ± SD
1	I	Drug	1.7333 ± 0.0715
		Blank	1.2372 ± 0.0322
2	II	Drug	1.9054 ± 0.0349
		Blank	1.5395 ± 0.0598
3	III	Drug	1.8739 ± 0.0072
		Blank	1.6480 ± 0.0681
4	IV	Drug	2.0363 ± 0.0617
		Blank	1.7222 ± 0.1105
5	V	Drug	1.0633 ± 0.0929
		Blank	0.8900 ± 0.0800
6	VI	Drug	1.4067 ± 0.0666
		Blank	1.1200 ± 0.1105

* Each value was an average of three determinations.

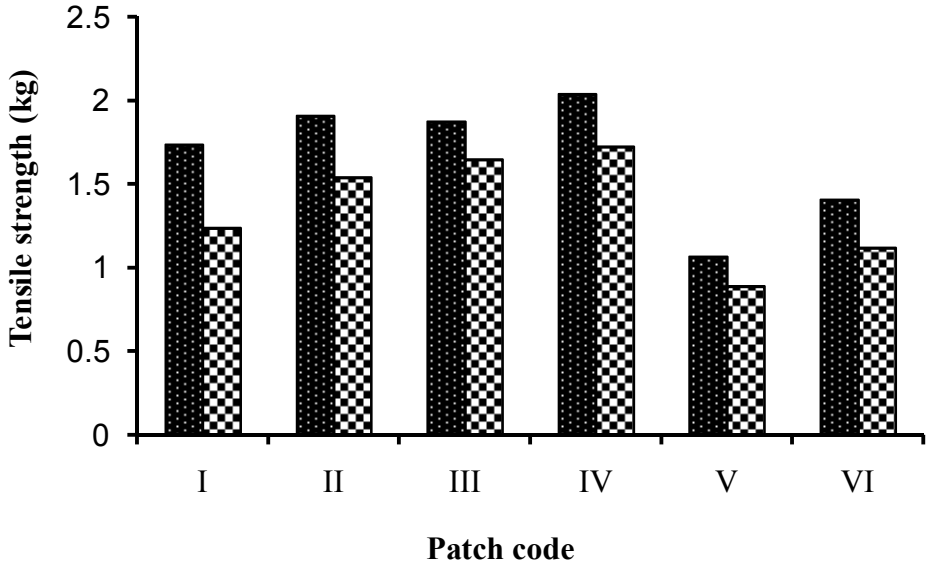


Figure 20: Tensile strength of patches determined using Universal strength testing machine for the blank and drug loaded patches.

Perusal to the Figure 20 indicated that the tensile strengths of drug loaded patches were higher than blank patches. This is justified because risperidone is slightly soluble and strengthened the bonding of polymer chains. The tensile strengths of drug loaded patches are in the order of IV >II >III >I >VI > V. This indicates HPMC chains produce effective cross-linking with ethyl cellulose. Among all the patches studied, patch IV showed highest tensile strength and patch V showed lowest tensile strength. This may be due the hydrogen bonding between drug and polymer.

Percentage elongation: Percentage elongation was determined using Universal strength testing machine for the blank and drug loaded films. The data are given in the Table 24 and depicted in the Figure 21. The order of percentage elongation of the film is IV > III > II > I >VI > V.

Table 24: Percentage elongation of risperidone patches

Sl. no.	Patch code		Percentage elongation* (%) AM ± SD
1	I	Drug	20.3333 ± 0.4638
		Blank	16.6898 ± 0.2626
2	II	Drug	22.7175 ± 0.7828
		Blank	21.7225 ± 0.4648
3	III	Drug	25.6442 ± 0.7358
		Blank	24.2542 ± 0.9348
4	IV	Drug	28.4667 ± 0.9882
		Blank	26.3525 ± 1.0883
5	V	Drug	15.6108 ± 0.6513
		Blank	15.0783 ± 1.2920
6	VI	Drug	17.1500 ± 2.0115
		Blank	14.6917 ± 1.2166

* Each value was an average of three determinations.

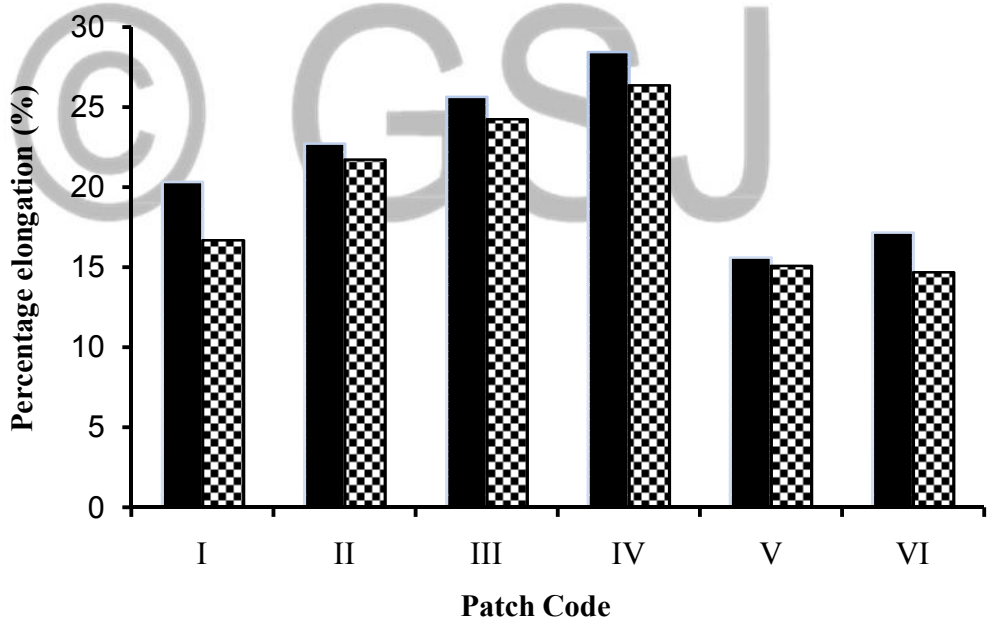


Figure 21: Percentage elongation of patches determined using Universal strength testing machine for the blank (dotted) and drug loaded patches (black filled).

Perusal to the Figure 21 indicated that the percentage elongation of drug loaded patches were higher than blank patches. This is justified because risperidone is slightly soluble and strengthened the bonding of polymer chains. The percentage

elongation of drug loaded patches is in the order of IV >II > III > I > VI > V. This indicates HPMC chains produce effective cross-linking. Among all the patches studied patch IV showed higher percentage elongation and patch V showed lower percentage elongation. All the drug loaded patches have shown higher percentage elongation compared to dummy patches. This may be due the hydrogen bonding between drug and polymer.

Percentage moisture loss: This test is of great significance as variation in moisture content causes a significant variation in mechanical properties of the film especially when film comprises of hygroscopic components. The capacity of the film to take up water is an important intrinsic parameter of the polymeric system in consideration to the release of drug. The data are given in the Table 25. Perusal to the Table 25 reveals that patches III and IV contain water insoluble polymer ethyl cellulose and therefore the percentage moisture loss is least. However, patches I and II exhibited highest loss due to water soluble polymer HPMC. In patches III and IV the loss decreased compared to patches I and II is because of the replacement of a part of HPMC by PVP.

Table 25: Percentage moisture of risperidone patches

Sl. no.	Patch Code	*Moisture loss (%) AM ± SD
1	I	9.6679 ± 0.5014
2	II	8.6637 ± 0.6774
3	III	5.9883 ± 0.6583
4	IV	4.1316 ± 0.7270
5	V	8.8509 ± 1.1528
6	VI	7.9639 ± 0.5712

* Each value was an average of three determinations.

Surface pH: The surface pH of all risperidone patches was within ± 0.3 units of the neutral pH and hence no mucosal irritation is expected. Ultimately patient compliance is achieved.

Folding endurance: Films did not show any cracks even after folding for more than 300 times. Hence it was taken as the end point. Folding endurance did not vary when the comparison was made between plain films and drug-loaded films.

Content uniformity of risperidone patches: The content uniformity tests are commonly employed for unit dosage forms such as tablets, capsules etc. In order to make sure about the uniform dispersion of drug in patches, content uniformity tests were carried out. The drug content was analysed at 270.6 nm. Corresponding blanks were used for the estimation of drug. The theoretical drug loading was 1 mg in 1x1 cm^2 patches.

The results of content uniformity tests are expressed as AM ± SD and reported in the Table 26. The results indicated that the drug was uniformly dispersed. Recovery was possible to the tune of 81.93 to 88.72. All the formulations showed more than 80% of the drug loading indicating much of the drug is not lost**.**

Table 26: Content uniformity of Risperidone patches

Patch code	Amount of drug present * (mg) AM ± SD	% Drug present
I	0.8486 ± 0.0034	84.86 ± 0.3415
II	0.8026 ± 0.0039	80.26 ± 0.3918
III	0.8872 ± 0.0440	88.72 ± 4.3960
IV	0.8746 ± 0.0189	86.46 ± 1.8892
V	0.8787 ± 0.0166	87.87 ± 1.6641
VI	0.8193 ± 0.0223	81.93 ± 2.2332

* Each reading was an average of three determinations.

Viscosity: Viscosity of polymer solutions was determined in LVDV-E Brookfield viscometer. Solutions of polymers were prepared same as those used for the preparation of films (working concentrations). The viscosities of the solutions are as shown in Table 27.

Table 27: Viscosity of polymers determined by Brookfield viscometer

Patch Code	Polymer (mg)		Solvent (ml)	*Viscosity (cps) AM ± SD
I	HPMC (15 cps)	250	Ethanol 8 ml	12.30 ± 0.4966
II	HPMC (47 cps)	250		18.07 ± 0.8213
III	HPMC (15 cps) Ethyl cellulose	200 50		23.19 ± 1.3285
IV	HPMC (47 cps) Ethyl cellulose	200 50		32.16 ± 2.2722
V	HPMC (47 cps) Poly vinyl pyrrolidone	200 50		13.26 ± 0.9514
VI	HPMC (15 cps) Poly vinyl pyrrolidone	200 50		20.91 ± 1.6786

*Each reading is an average of three determinations.

Viscosity of film IV was high when compared to others. It could be because of ethyl cellulose using as co-polymer where as viscosity is least in film I probably due to dispersion of polymer in ethanol. However there is a need to explore the relation between viscosity and other properties of films.

***In Vitro* Release Studies**

In vitro release studies of risperidone patches were carried out in phosphate buffer solution, pH 6.6. The release data of risperidone are given in the Tables 28 to 34, respectively for the patches I to VI. The details of calculations showing drug release from the patch V are shown in the Table 33 as a model.

Table 28: Data of *in vitro* release of risperidone from the patch I in the phosphate buffer solution, pH 6.6 at 37 ^{o}C.

Time (min)	Cumulative drug * released (mg) AM ± SD	% Drug released	% Drug remain unreleased	Log% drug remain unreleased
0	0.0000 ± 0.0000	0.00	100.00	2.0000
5	0.1651 ± 0.0075	19.42	80.58	1.9062
10	0.2159 ± 0.0171	25.40	74.60	1.8727
15	0.2926 ± 0.0365	34.42	65.58	1.8168
20	0.3538 ± 0.0255	41.62	58.38	1.7663
25	0.4286 ± 0.0275	50.43	49.57	1.6952
30	0.5139 ± 0.0210	60.46	39.54	1.5970
35	0.5988 ± 0.0522	70.45	29.55	1.4706
40	0.6793 ± 0.0462	79.92	20.08	1.3028
45	0.7625 ± 0.0261	89.71	10.29	1.0124
50	0.7985 ± 0.0247	93.94	6.06	0.7824
55	0.8260 ± 0.0261	97.17	2.83	0.4516

* Each reading is an average of 3 determinations.
Initial drug concentration = 0.85mg.

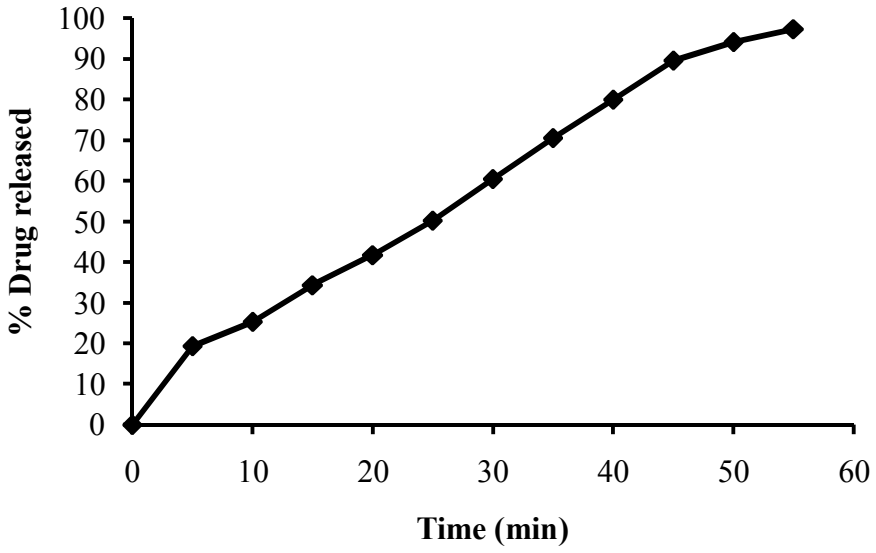


Figure 22: *In vitro* release of risperidone from the patch I in the phosphate buffer solution, pH 6.6.

Table 29: Data of *in vitro* release of risperidone from the patch II in the phosphate buffer solution, pH 6.6 at 37 ^{o}C.

Time (min)	Cumulative drug * released (mg) AM ± SD	% Drug released	% Drug remain unreleased	Log% drug remain unreleased
0	0.0000 ± 0.0000	0.00	100.00	2.0000
5	0.1701 ± 0.0189	21.26	78.74	1.8962
10	0.2111 ± 0.0192	26.39	73.61	1.8669
15	0.2513 ± 0.0249	31.41	68.59	1.8363
20	0.3017 ± 0.0282	37.71	62.29	1.7944
25	0.3565 ± 0.0260	44.57	55.43	1.7438
30	0.4147 ± 0.0201	51.84	48.16	1.6827
35	0.4687 ± 0.0375	58.59	41.41	1.6171
40	0.5371 ± 0.0220	67.14	32.86	1.5167
45	0.6316 ± 0.0304	78.96	21.04	1.3231
50	0.6948 ± 0.0154	86.85	13.15	1.1189
55	0.7386 ± 0.0121	92.32	7.68	0.8852
60	0.7607 ± 0.0114	95.08	4.92	0.6917
65	0.7787 ± 0.0110	97.33	2.67	0.4258

* Each reading is an average of three determinations.
Initial drug concentration= 0.80mg.

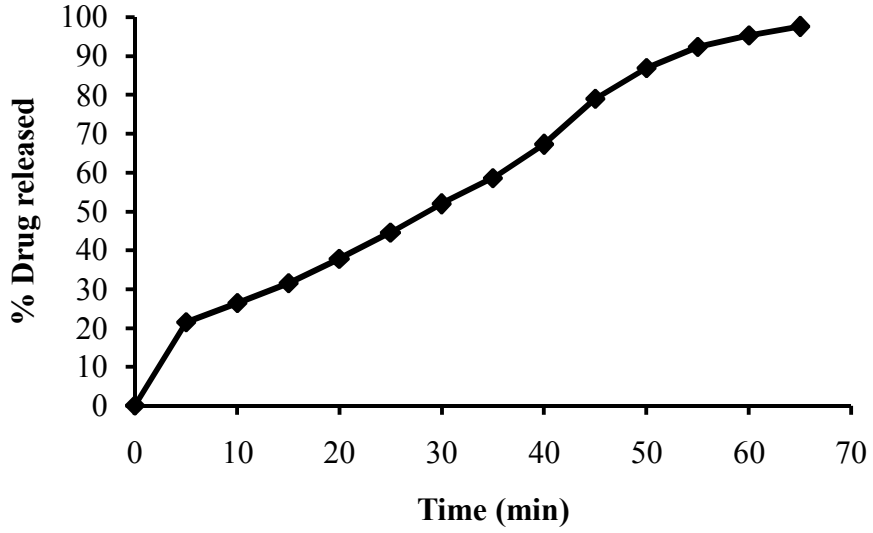


Figure 23: *In vitro* release of risperidone from the patch II in the phosphate buffer solution, pH 6.6.

Table 30: Data of *in vitro* release of risperidone from the patch III in the phosphate buffer solution, pH 6.6 at 37 ^{o}C.

Time (min)	Cumulative drug * released (mg) AM ± SD	% Drug released	% Drug remain unreleased	Log% drug remain unreleased
0	0.0000 ± 0.0000	0.00	100.00	2.0000
5	0.1488 ± 0.0398	16.72	83.28	1.9205
10	0.2063 ± 0.0660	23.18	76.82	1.8855
15	0.2650 ± 0.0572	29.78	70.22	1.8465
20	0.3149 ± 0.0731	35.39	64.61	1.8103
25	0.3730 ± 0.0674	41.91	58.09	1.7641
30	0.4407 ± 0.0744	49.52	50.48	1.7031
35	0.4960 ± 0.0723	55.73	44.27	1.6461
40	0.5456 ± 0.0661	61.30	38.70	1.5877
45	0.6266 ± 0.0692	70.41	29.59	1.4712
50	0.7219 ± 0.0718	81.11	18.89	1.2762
55	0.7806 ± 0.0535	87.71	12.29	1.0896
60	0.8296 ± 0.0256	93.21	6.79	0.8318
65	0.8570 ± 0.0183	96.29	3.71	0.5695
70	0.8704 ± 0.0138	97.80	2.20	0.3424

* Each reading is an average of three determinations.

Initial drug concentration= 0.89mg.

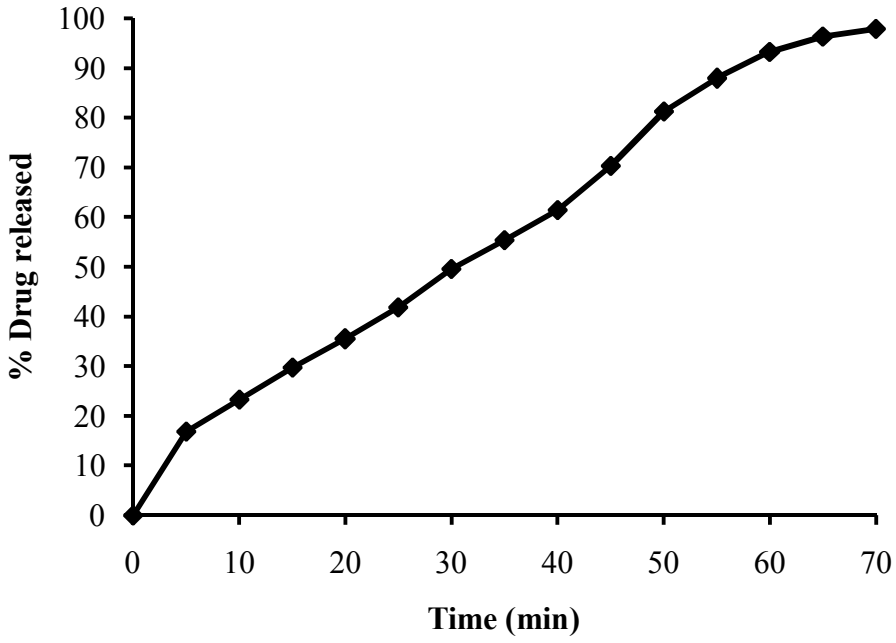


Figure 24: *In vitro* release of risperidone from the patch III in the phosphate buffer solution, pH 6.6.

Table 31: Data of *in vitro* release of risperidone from the patch IV in the phosphate buffer solution, pH 6.6 at 37 ^{o}C.

Time (min)	Cumulative drug * released (mg) AM ± SD	% Drug released	% Drug remain unreleased	Log% drug remain unreleased
0	0.0000 ± 0.0000	0.00	100.00	2.0000
5	0.1388 ± 0.0199	15.87	84.13	1.9250
10	0.1645 ± 0.0238	18.80	81.20	1.9095
15	0.1912 ± 0.0354	21.85	78.15	1.8929
20	0.2263 ± 0.0593	25.86	74.14	1.8701
25	0.2689 ± 0.0762	30.73	69.27	1.8405
30	0.3119 ± 0.1044	35.65	64.35	1.8085
35	0.3453 ± 0.1113	39.46	60.54	1.7820
40	0.4021 ± 0.1160	45.96	54.04	1.7327
45	0.4624 ± 0.1122	52.84	47.16	1.6736
50	0.5235 ± 0.1074	59.83	40.17	1.6039
55	0.5943 ± 0.1009	67.92	32.08	1.5062
60	0.6576 ± 0.1070	75.15	24.85	1.3953
65	0.7079 ± 0.0950	80.90	19.10	1.2810
70	0.7644 ± 0.0777	87.36	12.64	1.1017
75	0.8262 ± 0.0374	94.42	5.58	0.7464
80	0.8434 ± 0.0367	96.39	3.61	0.5576

* Each reading is an average of three determinations.
Initial drug concentration= 0.875mg.

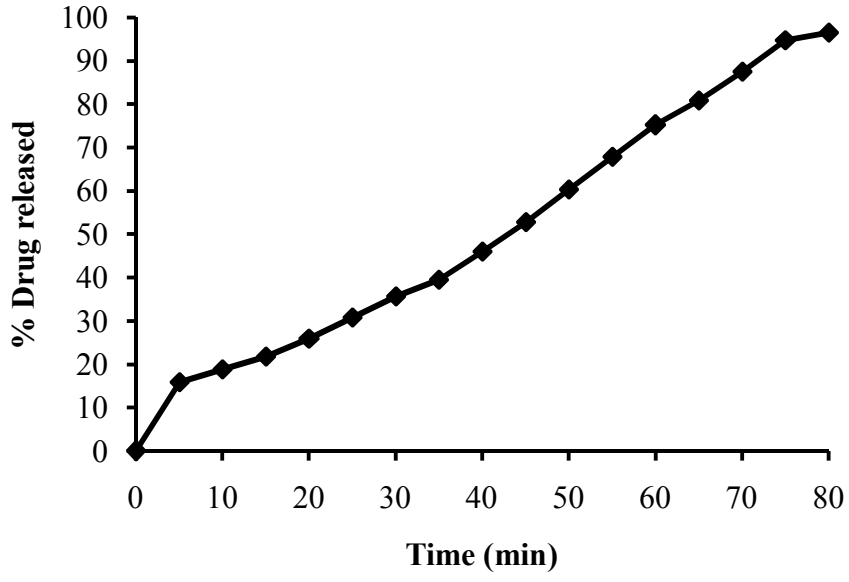


Figure 25: *In vitro* release of risperidone from the patch IV in the phosphate buffer solution, pH 6.6.

Table 32: Data of *in vitro* release of risperidone from the patch V in the phosphate buffer solution, pH 6.6 at 37 ^{o}C.

Time (min)	Cumulative * drug released (mg) AM + SD	% Drug released	% Drug remain unreleased	Log% drug remain unreleased
0	0.0000 ± 0.0000	0.0000	100.0000	2.0000
5	0.2477 ± 0.0234	28.1426	71.8574	1.8565
10	0.3313 ± 0.0234	37.6514	62.3486	1.7948
15	0.4086 ± 0.0471	46.4282	53.5718	1.7289
20	0.5089 ± 0.0618	57.8273	42.1727	1.6250
25	0.5595 ± 0.0825	63.5767	36.4233	1.5614
30	0.6365 ± 0.0751	72.3250	27.6750	1.4421
35	0.7048 ± 0.0659	80.0927	19.9073	1.2990
40	0.7690 ± 0.0469	87.3842	12.6158	1.1009
45	0.8437 ± 0.0211	95.8696	4.1304	0.6160
50	0.8630 ± 0.0157	98.0656	1.9344	0.2866

* Each reading is an average of three determinations.
Initial drug concentration = 0.88mg

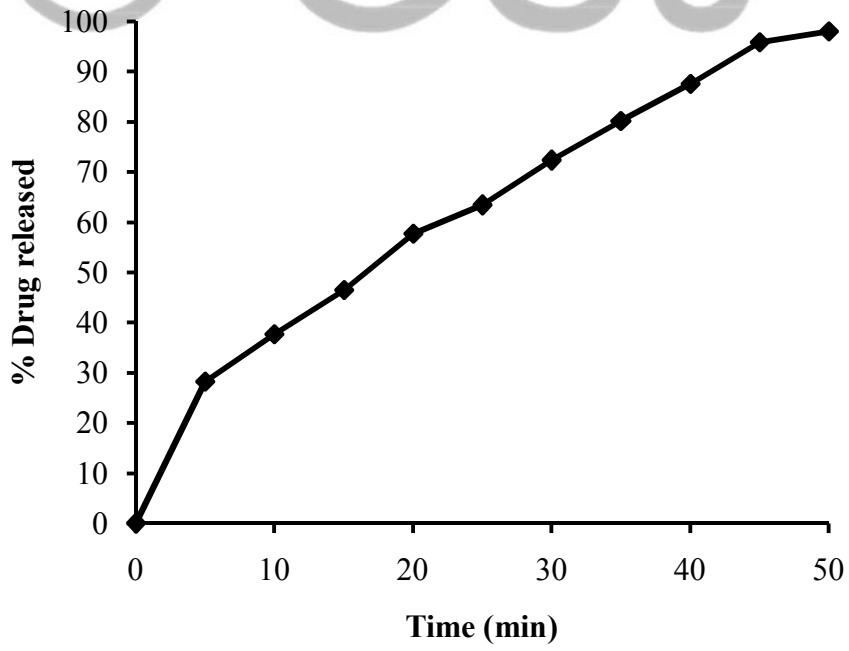


Figure 26: *In vitro* release of risperidone from the patch V in the phosphate buffer solution, pH 6.6.

Table 33: Detailed calculation of dissolution profile for optimized formula

Time (min)	Abs.	Conc. (mcg/ml)	Conc. in 5ml (mcg/ml)	Conc. in 5ml (mg/ml)	Conc. in 100 ml (mg/ml)	Cumulative drug release (mg/ml)	% drug released	AM ± SD
5	0.059	2.2139	11.0694	0.0111	0.2214	0.2214	25.16	28.14 ± 2.6629
	0.071	2.6642	13.3208	0.0133	0.2664	0.2664	30.27	
	0.068	2.5516	12.7580	0.0128	0.2552	0.2552	29.00	
10	0.079	2.9644	14.8218	0.0148	0.2964	0.3075	34.94	37.65 ± 2.6560
	0.085	3.1895	15.9475	0.0159	0.3189	0.3323	37.76	
	0.091	3.4146	17.0732	0.0171	0.3415	0.3542	40.35	
15	0.090	3.3771	16.8856	0.0169	0.3367	0.3636	41.32	46.43 ± 5.3557
	0.100	3.7523	18.7617	0.0188	0.3752	0.4045	45.97	
	0.114	4.2777	21.3884	0.0214	0.4278	0.4576	52.00	
20	0.110	4.1276	20.6379	0.0206	0.4128	0.4555	51.77	57.83 ± 7.0187
	0.119	4.4653	22.3265	0.0223	0.4465	0.4946	56.20	
	0.140	5.2533	26.2664	0.0263	0.5253	0.5765	65.52	
25	0.109	4.0901	20.4503	0.0205	0.4090	0.4724	53.68	63.58 ± 9.3788
	0.133	4.9906	24.9531	0.0250	0.4991	0.5694	64.71	
	0.149	5.5910	27.9550	0.0280	0.5591	0.6366	72.34	
30	0.126	4.7280	23.6398	0.0236	0.4728	0.5567	63.26	72.33 ± 8.5369
	0.147	5.5159	27.5797	0.0276	0.5516	0.6469	73.51	
	0.160	6.0038	30.0188	0.0300	0.6004	0.7058	80.21	
35	0.140	5.2533	26.2664	0.0263	0.5253	0.6328	71.91	80.09 ± 7.4858
	0.159	5.9662	29.8311	0.0298	0.5966	0.7195	81.76	
	0.167	6.2664	31.3321	0.0313	0.6266	0.7621	86.60	
40	0.156	5.8537	29.2683	0.0293	0.5854	0.7191	81.72	87.38 ± 5.3275
	0.166	6.2289	31.1445	0.0311	0.6229	0.7756	88.14	
	0.172	6.4540	32.2702	0.0323	0.6454	0.8122	92.29	
45	0.175	6.5666	32.8330	0.0328	0.6567	0.1630	93.15	95.87 ± 2.3974
	0.178	6.6792	33.3959	0.0334	0.6679	0.8518	96.79	
	0.176	6.6041	33.0206	0.0330	0.6604	0.8595	97.67	
50	0.173	6.4916	32.4578	0.0325	0.6492	0.8450	96.03	98.07 ± 1.7805
	0.175	6.5666	32.8330	0.0328	0.6567	0.8739	99.31	
	0.170	6.3790	31.8949	0.0319	0.6379	0.8700	98.86	

AM = Arithmetic mean ; SD = Standard deviation

Table 34: Data of *in vitro* release of risperidone from the patch VI in the phosphate buffer solution, pH 6.6 at 37 ^{o}C.

Time (min)	Cumulative drug * released (mg) AM ± SD	% Drug released	% Drug remain unreleased	log% drug remain unreleased
0	0.0000 ± 0.0000	0.00	100.00	2.0000
5	0.1889 ± 0.0282	23.03	76.97	1.8863
10	0.2496 ± 0.0178	30.44	69.56	1.8424
15	0.3066 ± 0.0211	37.39	62.61	1.7966
20	0.3559 ± 0.0381	43.40	56.60	1.7528
25	0.4182 ± 0.0361	51.00	49.00	1.6902
30	0.4916 ± 0.0372	59.95	40.05	1.6026
35	0.5652 ± 0.0528	68.92	31.08	1.4924
40	0.6301 ± 0.0411	76.85	23.15	1.3646
45	0.7159 ± 0.0284	87.31	12.69	1.1034
50	0.8035 ± 0.0077	97.99	2.01	0.3036
55	0.8114 ± 0.0081	98.96	1.04	0.0184

* Each reading is an average of three determinations.
Initial drug concentration = 0.82mg.

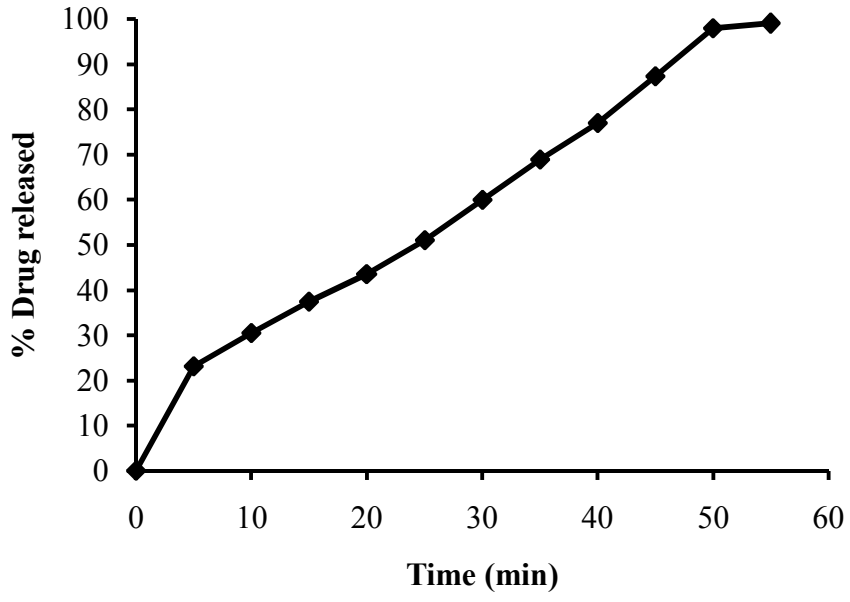


Figure 27: *In vitro* release of risperidone from the patch VI in the phosphate buffer solution, pH 6.6.

The *in vitro* release data of risperidone from all the patches are compiled in the Table 35. Drug release profiles from all the patches are shown in the Figure 28. A perusal to the Figure 28 and the Table 35 indicated that the release of risperidone decreased when the viscosity of HPMC is increased. Ethylcellulose retarded the release rate of drug from HPMC patches (patches III and IV). PVP increased the drug release rate from HPMC films. Perusal to the Tables 29 and 34 indicated that PVP increases the drug release rate from HPMC 47 cps films though the effect is less in the initial periods.

The results of drug release can be correlated with the percent moisture loss. Percent moisture loss is an indication of the capacity of polymer to retain moisture content. More the moisture retention in the patches more could be the tendency of drug release.

Viscosity of the polymer also has its influence on the drug release rate. If the viscosity of the polymeric solution is more, then drug release rate will also be more.

Table 35: Compilation of *in vitro* release of risperidone at 30 min

Sl. No.	Patch code	% Drug released
1	I	60.46
2	II	51.84
3	III	49.52
4	IV	35.64
5	V	72.33
6	VI	40.05

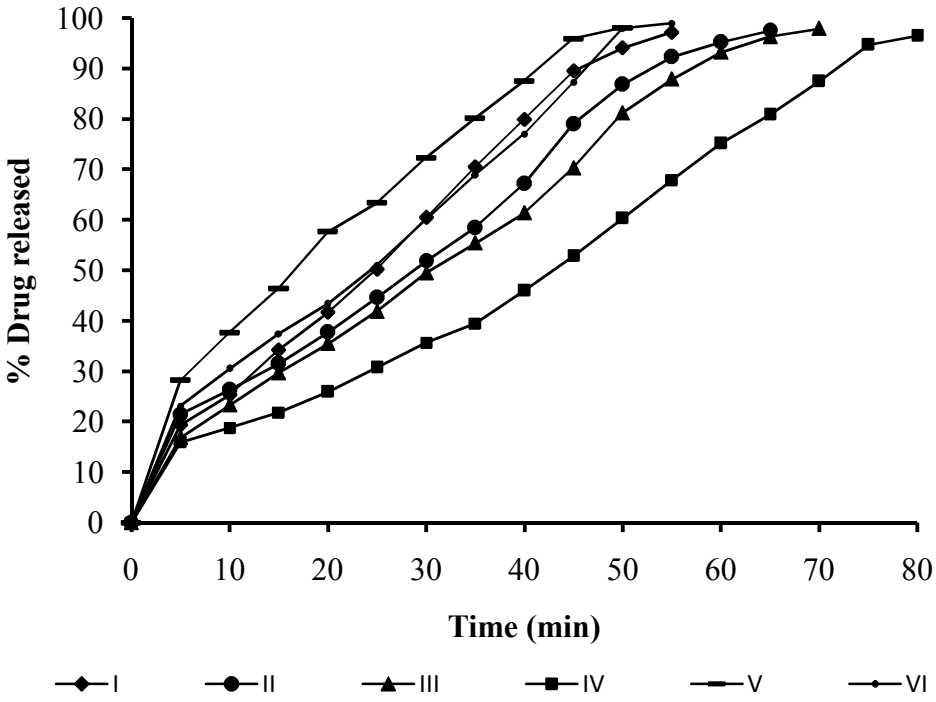


Figure 28: *In vitro* release of risperidone from patches I to VI.

Kinetics of Drug Release (Zero and First Order)

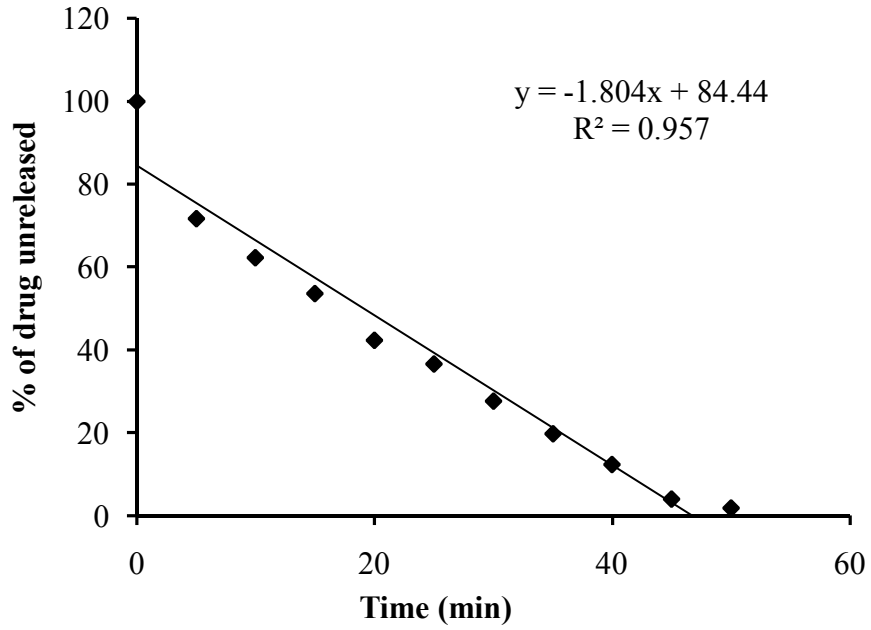


Figure 29: *In vitro* release of risperidone from patch V in phosphate buffer (pH6.6).

Zero order release

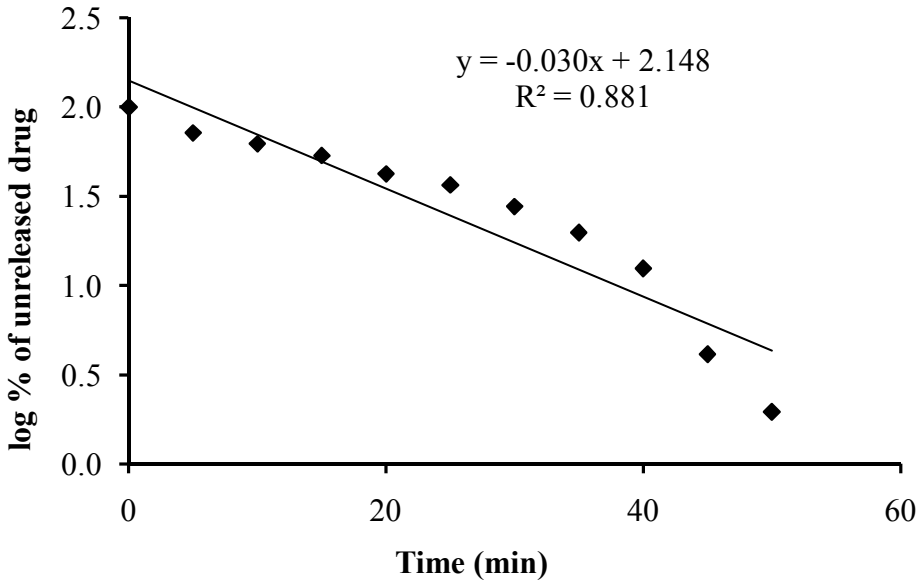


Figure 30: *In vitro* release of risperidone from patch V in phosphate buffer (pH 6.6).

First order release

Data of in vitro drug-release were fit into different equations and kinetic models to explain the release kinetics of risperidone from these patches. The release data of risperidone from the patch V are processed into graphs as shown in the Figures 29 and 30 to understand the linear relationship (kinetic principles), as models. The data of all the patches were processed for regression analysis using MS-Excel statistical functions. The parameters and equations are given in the Table 36.

A perusal to the Table 36 indicated that the regression values are higher with zero order and therefore the release kinetics of risperidone followed zero order from all the patches.

Table 36: Comparison of orders of *in vitro* release of risperidone from patches I - VI.

Patch Code	*In vitro* release in Phosphate buffer pH 6.6 Regression equations	
	Zero order	**First order**
I	y = -1.759x + 93.19 R^2 = 0.988	Log y = -0.025x + 2.180 R^2 = 0.887
II	y = -1.468x + 91.30 R^2 = 0.982	Log y = -0.022x + 2.184 R^2 = 0.882
III	y = -1.392x + 92.77 R^2 = 0.988	Log y = -0.021x + 2.208 R^2 = 0.87
IV	y = -1.176x + 97.08 R^2 = 0.988	Log y = -0.015x + 2.178 R^2 = 0.823
V	y = -1.804x + 84.44 R^2 = 0.957	Log y =-0.030x + 2.148 R^2 = 0.881
VI	y = -1.708x + 90.69 R^2 = 0.984	Log y = -0.030x + 2.254 R^2 = 0.776

Release Mechanisms

To understand the release mechanisms of risperidone, the data of *in vitro* drug release were fit into Higuchi's model and Hixon-Crowell cube root law model. The data of *in vitro* drug release from the patch V are fit into the models specified and the graphs are generated as shown in the Figures 32 (Higuchi's model) and 33 (Hixson-Crowel model), as representative figures. However the equations generated for all the patches are shown in the Table 38.

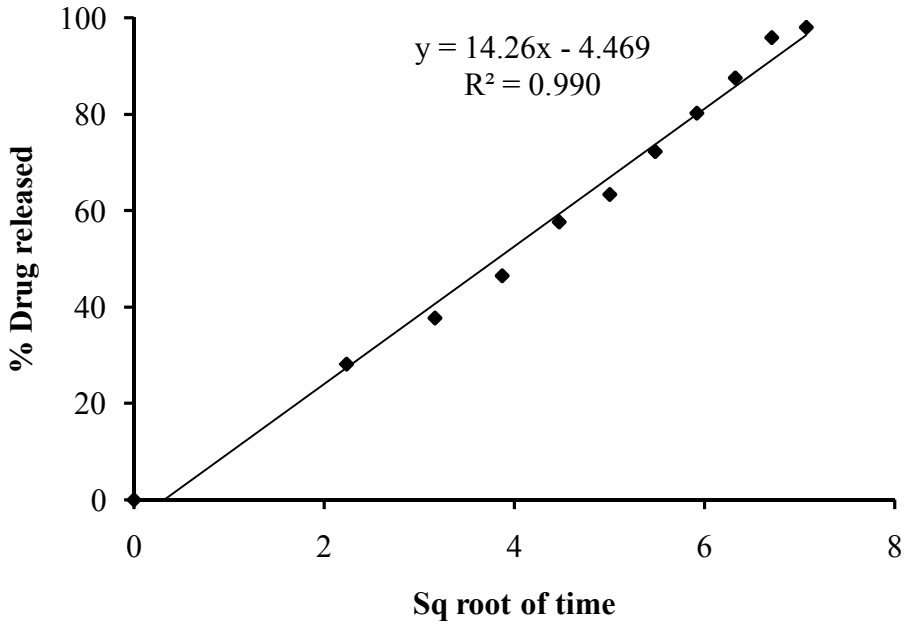


Figure 31: *In vitro* release of risperidone from patch V in phosphate buffer (pH 6.6).

Higuchi's Release Model

Table 37: Fitting of the Hixon-Crowell cube root law for *in vitro* release of risperidone from Patch V.

Time in min	$M_0^{1/3} - M^{1/3}$	K, $mg^{1/3}$/min
0	0.0	0.0000
5	0.0997	0.0199
10	0.1393	0.0139
15	0.1797	0.0120
20	0.2394	0.0120
25	0.2736	0.0109
30	0.3335	0.0111
35	0.3985	0.0114
40	0.4774	0.0119
45	0.6267	0.0139
50	0.7008	0.0140
For patch V (M_0 = 0.880mg)		Mean K = 0.0119

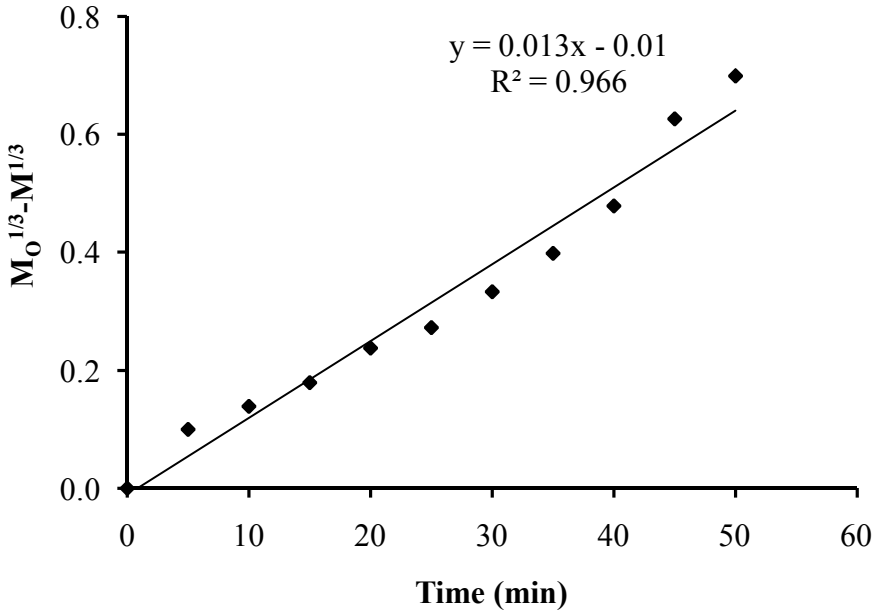


Figure 32: Fitting of the Hixon-Crowell cube root law for *in vitro* release of risperidone from patch V.

Table 38: Regression equations of *in vitro* release of risperidone from patches I - VI.

Patch code	Hixon-Crowell model	Higuchi's model
I	y = 0.011x - 0.042 R² = 0.959	y = 14.17x - 12.89 R² = 0.949
II	y = 0.009x - 0.049 R² = 0.943	y = 13.04x - 12.02 R² = 0.947
III	y = 0.009x - 0.049 R² = 0.949	y = 12.88x - 14.30 R² = 0.949
IV	y = 0.007x - 0.053 R² = 0.913	y = 11.75x - 8.206 R² = 0.988
V	**y** = 0.013x - 0.01 R² = 0.966	y = 14.26x - 4.469 R² = 0.990
VI	y = 0.012x - 0.048 R² = 0.905	y = 13.81x - 10.07 R² = 0.953

Application of Hixon – Crowell cube root law, the equation $(M_0^{1/3} - M^{1/3}) = kt$, provides information about the release mechanism, namely dissolution rate limited. Application of Higuchi's equation ($M = K\ t^{1/2}$) provides information about the release mechanism, namely diffusion rate limited.

Perusal to Table 38 indicates that R^2 values are higher for Higuchi's model compared to Hixon – Crowell for all the patches. Hence risperidone release from the all the patches followed diffusion rate controlled mechanism.

***In vivo* Absorption of Risperidone in Rabbit Buccal Mucosa from Patches**

Patch V out of six formulations prepared was considered as the best formulation based on the *in vitro* release rate. Therefore, this formulation was selected for the *in vivo* studies. The *in vivo* absorption studies were conducted on rabbits for the patches V. The method used for this purpose was the measurement of disappearance of the drug from the patches. Data are recorded in the Table 39. Each recording was an average of three determinations. About 84.59% of risperidone was absorbed from patch V within 30 min (Figure 33).

Table 39: *In vivo* absorption of risperidone in rabbit buccal mucosa from patch V.

Time (min)	%Drug absorbed (mg)	Log % drug absorbed	% drug unabsorbed	Log % drug unabsorbed
0	0.00	0.0000	100.00	2.0000
10	45.02	1.6518	54.98	1.7391
20	71.20	1.8524	28.80	1.4585
30	84.59	1.9270	15.41	1.1792

* Each reading is an average of three determinations.
Initial amount of drug = 0.880 mg.

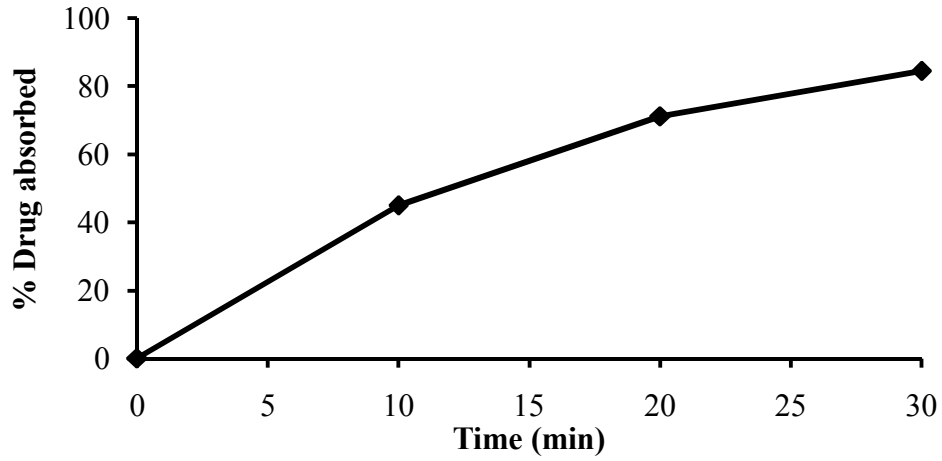


Figure 33: *In vivo* absorption of risperidone in rabbit buccal mucosa from patch V.

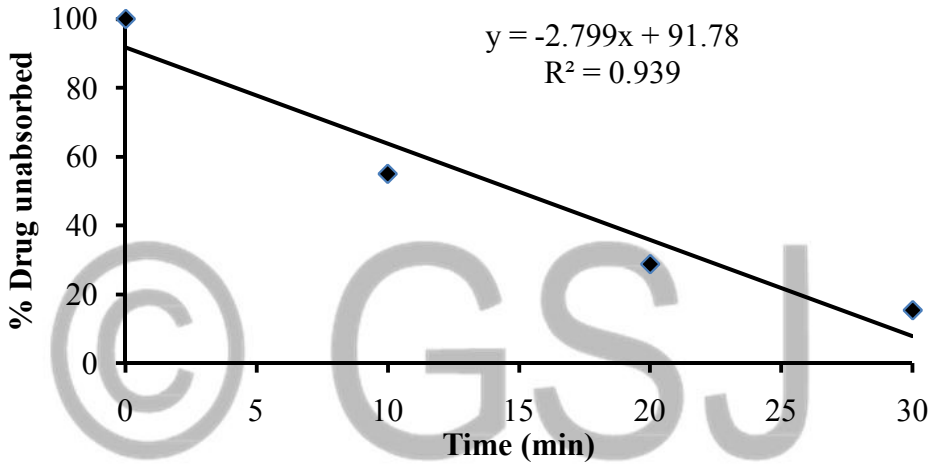


Figure 34: *In vivo* absorption of risperidone in rabbit buccal mucosa from patch V.

Zero order absorption

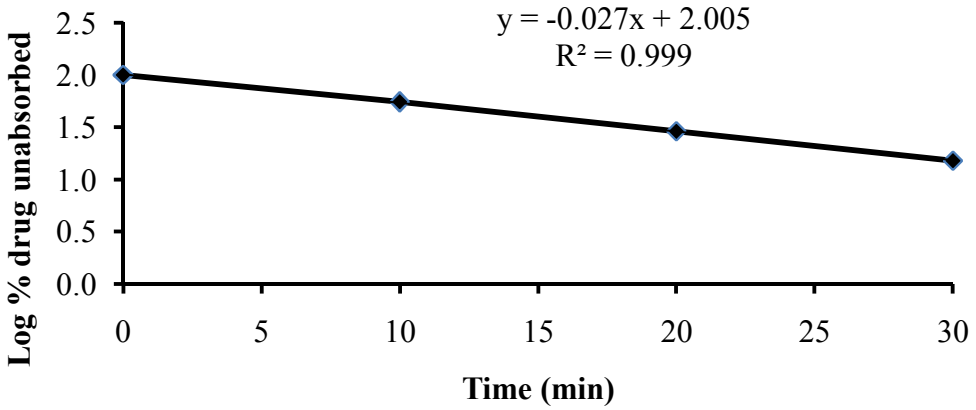


Figure 35: *In vivo* absorption of risperidone in rabbit buccal mucosa from patch V.

First order absorption

Kinetics of Absorption of Risperidone through Rabbit Buccal Mucosa

The absorption data for risperidone (Table 40) were processed into graphs (Figures 34 and 35) to understand the linear relationship i.e., kinetic principles. The data were processed for regression analysis and the equations were given in the Table 40. A perusal to the Table 40 indicated that the buccal absorption of risperidone from rabbit buccal mucosa followed first order from patch V.

Table 40: Comparison of orders of *in vivo* absorption of risperidone from patch V in rabbit buccal mucosa.

Formulation	***In vivo* buccal absorption, Regression equations**	
	Zero order	**First order**
Patch V	Y = -2.799x + 91.78 R^2 = 0.939	log y = -0.027x + 2.005 R^2 = 0.999

***In Vivo* Absorption of Risperidone from Patch V in Human Volunteers**

In vivo absorption studies were conducted on human volunteers.[48] In this test, *in vivo* drug release was estimated than *in vivo* absorption for simplifying the method. Therefore, this test gives an indirect evidence of extent of absorption of drug from the patches. Risperidone has an intrinsic ability to get absorbed from buccal mucosa, which was evidenced by buccal absorption test. The data of the tests were recorded in the Table 41. The study revealed that, the release of risperidone from the patches is appreciable.

Table 41: *In vivo* absorption of risperidone in human buccal mucosa from patch V.

Time (min)	%Drug absorbed (mg)	Log % drug absorbed	% drug unabsorbed	Log % drug unabsorbed
0	0.00	0.0000	100.0000	2.0000
10	37.03	1.5654	62.9655	1.7980
20	68.76	1.8367	31.2411	1.4914
30	80.78	1.9071	19.2166	1.2794

* Each reading is an average of three determinations.
Initial amount of drug = 0.880 mg.

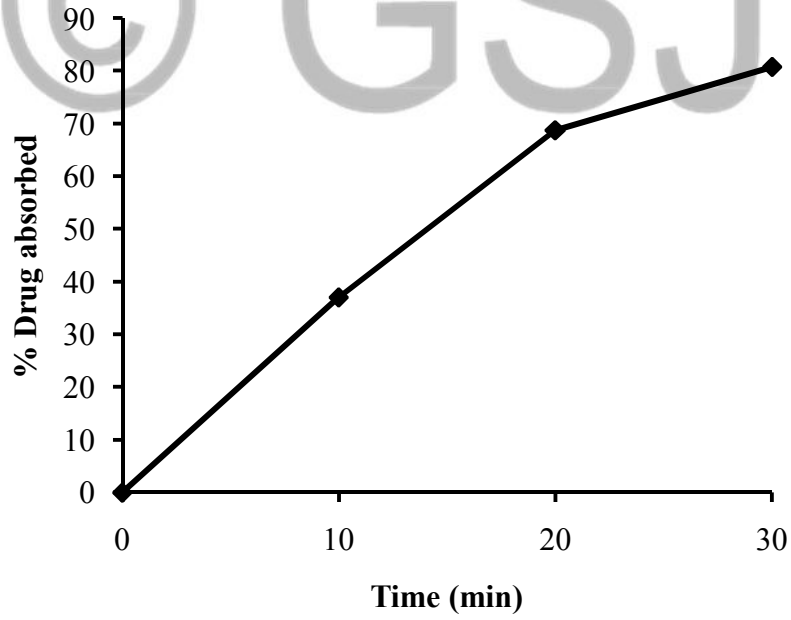


Figure 36: *In vivo* absorption of risperidone in human buccal mucosa from patch V.

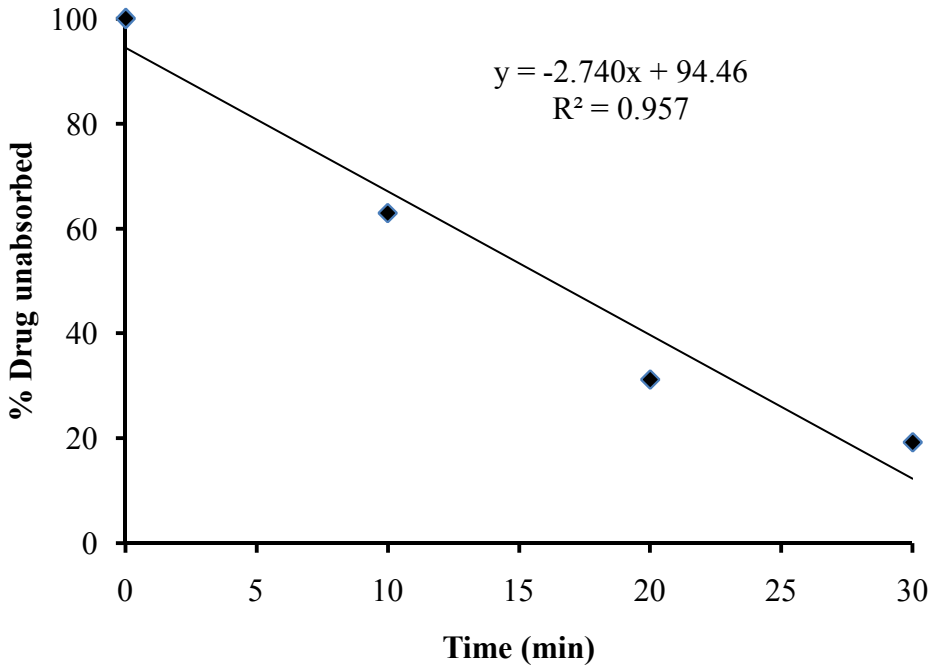


Figure 37: *In vivo* absorption of risperidone in human buccal mucosa from patch V.

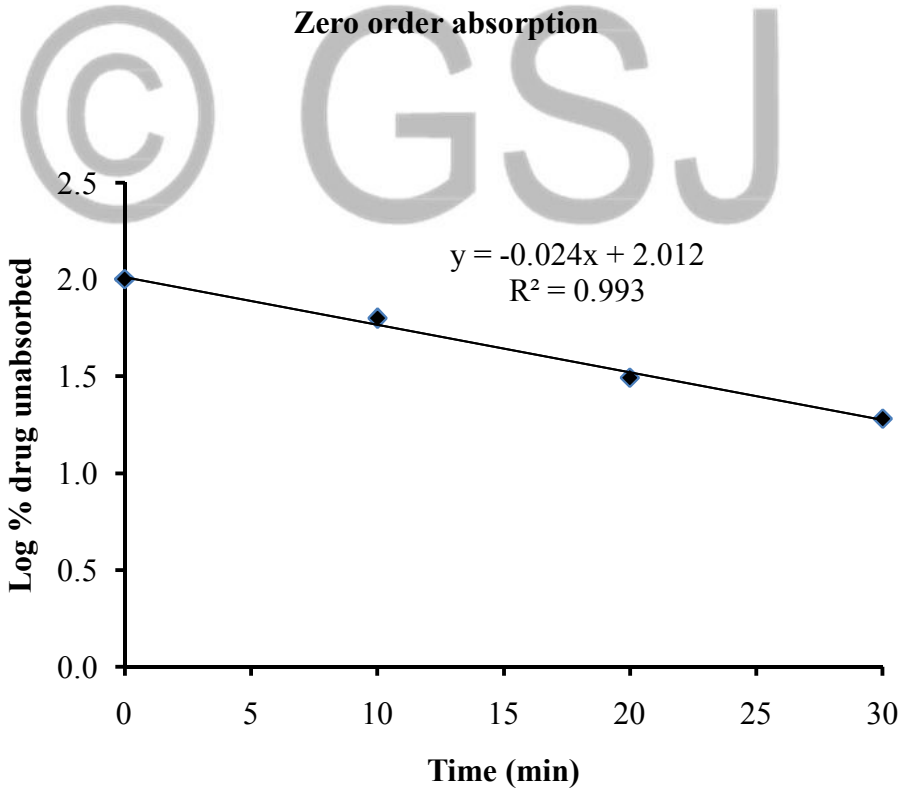


Figure 38: *In vivo* absorption of risperidone in human buccal mucosa from patch V.

First order absorption

The absorption data for risperidone (Table 40) were processed into graphs (Figures 37 and 38) to understand the linear relationship i.e., kinetic principles. The data were processed for regression analysis and the equations were given in the Table 41. A perusal to the Table 41 indicated that the buccal absorption of risperidone from human buccal mucosa followed first order from patch V. The results are in tune with the *in vivo* studies in rabbits.

During *in vivo* patch test, none of the films had to be removed due to irritation. The films did not cause any discomfort to the volunteers. No side effects like taste alteration, heaviness, dry mouth, or severe salivation were observed. The system claims the potential clinical usefulness in delivering the drug.

***In Vitro In Vivo* Correlation (IVIVC)**

The concept of *in vitro* - *in vivo* correlation has been extensively used by pharmaceutical scientists. *In vitro* release studies and their correlation with *in vivo* studies will be helpful to predict therapeutic efficiency of the dosage form. So correlation between *in vitro* release behavior of a drug and it's *in vivo* absorption in rabbits must be demonstrated experimentally to reproduce therapeutic response.

***In vitro* release vs. *in vivo* rabbit buccal absorption of risperidone from patch V:** The relevant data were taken from the Tables 32 and 39, for the *in vitro* release and *in vivo* buccal absorption for the patch V. The data obtained were recorded in Table 42. Further the data were regressed using MS-Excel statistical program. A perusal to the Figure 39 indicated good correlation (R^2 = 0.996) for patchV.

Table 42: *In vitro* release vs. *in vivo* rabbit buccal absorption of risperidone from patch V.

Time (min)	*In vitro* drug release (%)	Time (min)	*In vivo* drug absorption (%)
0	00.00	0	0.00
10	34.94	10	45.02
20	57.71	20	71.20
30	72.33	30	84.59

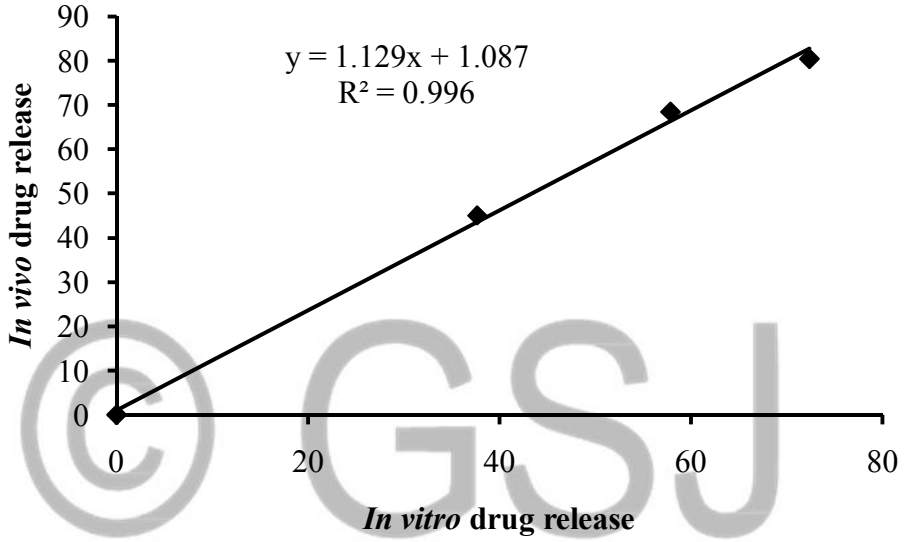


Figure 39: *In vitro* release Vs *in vivo* rabbit buccal absorption of risperidone from patch V

Ageing

Optimized medicated patches were subjected to short term stability testing. Patches were placed in a glass beaker lined with aluminium foil and maintained at 40 ± 2 °C and 75 ± 5% RH for 1 month as per ICH guidelines.[48] Apart from this, the patches were also exposed to room conditions for 1 month. The patches were observed for their appearance and texture. These properties did not change during the period of the study. Changes in the drug content of the stored patches were investigated during storage. The data presented were the mean of three

determinations. Percentage drug present in the patches was determined spectrophotometrically and reported in the Table 43 and represented in the Figure 40. Percentage decrease in drug content in all the patches was also calculated and reported in the Table 43 and represented in the Figure 41. Perusal to the Tables 43 to 46 and the Figures 40 to 43 indicated that the drug loss is less though the patches were stored for one month. Further there is a need of accelerated stability testing of these dosage forms to determine their shelf life. Buccal mucoadhesive patches containing risperidone showed satisfactory characteristics without being drastically influenced by ageing.

Table 43: Percentage drug present in risperidone patches

Time (weeks)	Patch I	Patch II	Patch III	Patch IV	Patch V	Patch VI
0	85.69	81.12	88.61	87.87	88.24	80.82
1	85.24	80.75	88.61	87.34	88.46	81.42
2	85.39	80.30	87.57	86.97	88.09	80.07
3	84.42	79.85	86.89	86.37	87.27	79.93
4	84.34	80.00	86.52	86.07	86.74	79.55

* Each reading is an average of three determinations.

Table 44: Percentage drug decrease in risperidone patches during one month

Patch Code	% Drug decrease
I	1.35
II	1.12
III	2.10
IV	1.80
V	1.50
VI	1.27

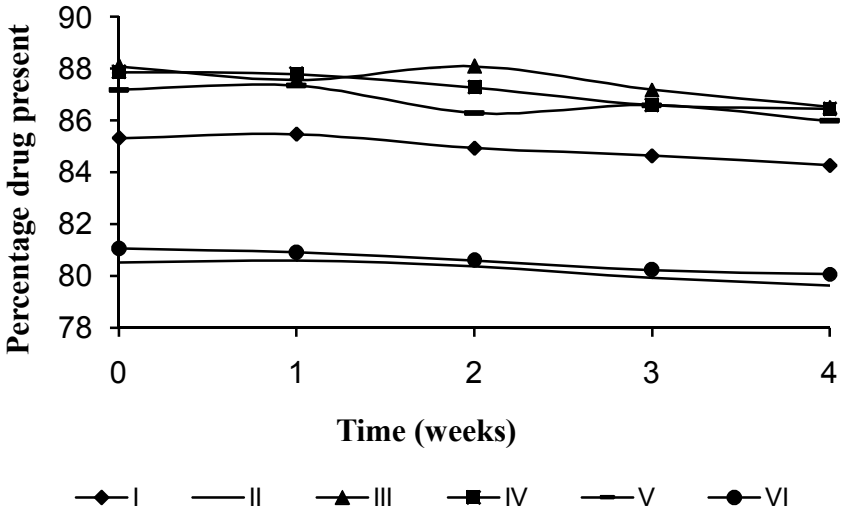


Figure 40: Percentage drug present in risperidone patches (I to VI) during one month storage.

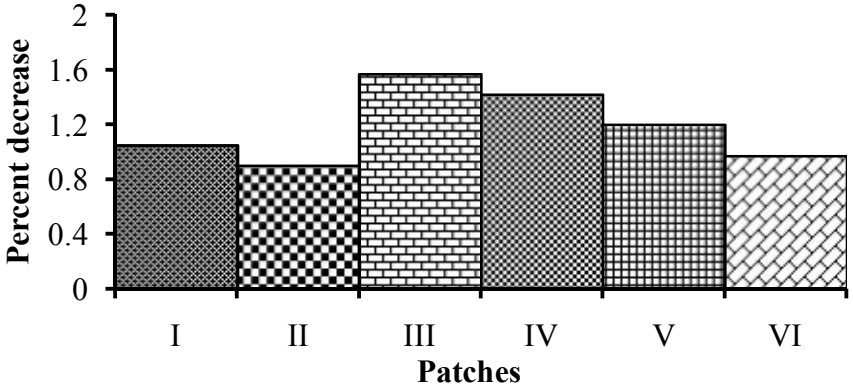


Figure 41: Percentage drug decrease in risperidone patches during one month storage

Table 45: Percentage drug present in risperidone patches (Under room conditions for one month)

Time (weeks)	Patch I	Patch II	Patch III	Patch IV	Patch V	Patch VI
0	85.32	80.52	88.09	87.87	87.19	81.05
1	85.47	80.60	87.57	87.79	87.34	80.90
2	84.94	80.37	88.09	87.27	86.29	80.60
3	84.64	79.93	87.19	86.59	86.59	80.22
4	84.27	79.63	86.52	86.44	85.99	80.07

* Each reading is an average of three determinations.

Table 46: Percentage drug decrease in risperidone patches during one month (Under room conditions)

Patch Code	% Drug decrease
I	1.05
II	0.90
III	1.57
IV	1.42
V	1.20
VI	0.97

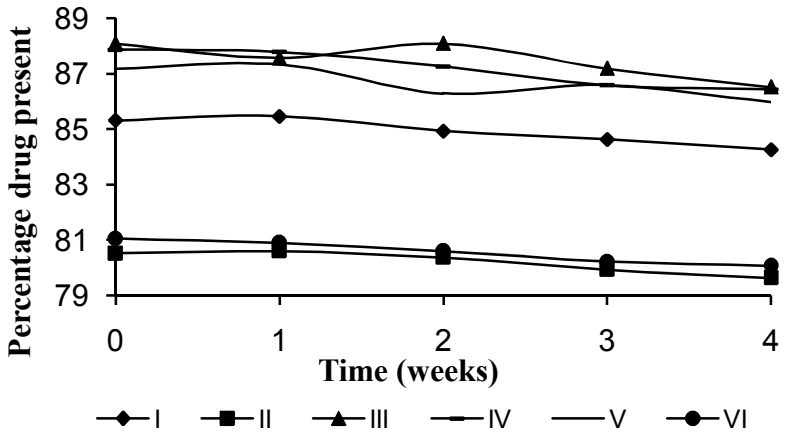


Figure 42: Percentage drug present in risperidone patches (I to VI) during one month storage under room conditions.

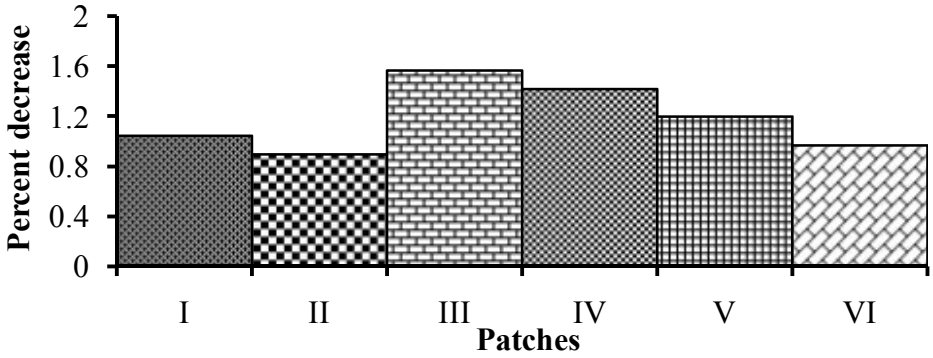


Figure 43: Percentage drug decrease in risperidone patches during one month storage under room conditions.

From the results obtained from the methods were the discussion generated from them, encouraged conclusions were drawn and presented in the next chapter "conclusions".

Conclusions

CONCLUSIONS

The conclusions drawn from the present investigation are given below.

1) Suitable analytical methods based on *UV-Vis* spectrophotometry were developed for risperidone.
2) The buccal absorption test was conducted on human volunteers to verify the extent of absorption of risperidone through buccal route. About 26.10% of the administered dose (1 mg) of risperidone was absorbed in 5 min. The results were encouraging.
3) Mucoadhesive patches of risperidone containing 1 mg of drug were prepared successfully using HPMC (15 & 47 cps), PVA, and ethyl cellulose polymers in different combinations and there were total seven films were prepared. Based on observations, six formulations were selected and used for further analysis. The films exhibited satisfactory characteristics regarding to integrity, flexibility, dispersion of drug, and other quality control parameters. Additives such as glycerin (plasticizer) and Tween-80 (dispersing agent) were included in the formulations.
4) The *in vitro* release of risperidone from the patches I to VI was in the range of 35.64 to 72.33% in 30 min, in phosphate buffer solution, pH 6.6. The release kinetics indicated zero order release from all the patches.
5) Higuchi's diffusion model and Hixon-Crowell cube root law were applied to test the release mechanism. R^2 values are higher for Higuchi's model compared to Hixon – Crowell model for all the patches. Hence risperidone release from the patches followed diffusion rate controlled.

6) The *in vivo* buccal absorption kinetics in rabbits indicated that about 80.40% of the drug was absorbed in 30 min from the patch V. The absorption kinetics was studied by regression analysis (R^2 =0.999). The absorption of risperidone followed first order.

7) The *in vivo* buccal absorption kinetics in human volunteers indicated that about 80.78% of the drug was absorbed in 30 min from the patches. It indicates that the risperidone has an intrinsic ability to absorb from buccal mucosa. Drug absorption followed first order and is in tune with rabbits buccal absorption.

8) The *in vitro-in vivo* correlations (IVIVC) were attempted for the release and absorption of risperidone patches. The correlation coefficient for patch V was 0.996.

Further work in this direction is needed in order to improve the absorption of risperidone from patches, probably by including the permeability enhancers, pH modifiers, and other additives.

Summary

SUMMARY

The summary of the M. Pharm. dissertation work entitled "**Design and Evaluation of Risperidone Buccal Mucoadhesive Patches**" is given below.

Introduction

In view of patients and clinicians oral route is perhaps the most preferred amongst various routes of drug delivery. However, this route possesses some problems for a few categories of drugs. The enzymes in the GI fluids, GIT-pH conditions, the enzymes bound to GIT membranes and enzymes present in the liver (First pass metabolism) are a few factors responsible for the bioavailability problems.

The oral cavity is highly acceptable by patients. The mucosa is relatively permeable with a rich blood supply. The oral transmucosal drug delivery bypasses first pass effect and avoids pre-systemic elimination in the GI tract. These factors make the oral mucosa a very attractive and feasible site for systemic drug delivery. Buccal mucosa also gives rapid absorption of drugs than oral route. A few drugs have been successfully administered via buccal route. For example, buccal buprenorphine works as rapidly as sublingual buprenorphine. Other examples are nicotine, morphine, propranolol etc.

Objectives

The objectives of the present investigation are**:**

1. To develop analytical method for the estimation of risperidone in a suitable solvent system.
2. To carry out preformulation studies for the drug, polymers, and blends.

3. To design a suitable buccal mucoadhesive delivery system (films) for risperidone using mucoadhesive polymers.
4. To evaluate the dosage forms (films) for the integrity and stability.
5. To study *in vitro* release of drug from the dosage forms.
6. Preliminary studies on *in vivo* absorption for a short time.

Several polymers have been identified for mucoadhesive properties. In the present investigation, HPMC-15cps, HPMC-47cps, ethyl cellulose, and poly vinyl pyrolidone (PVP) were used.

The drug chosen for the present investigation is risperidone, an anti-psychotic agent. More than half of an oral dose of risperidone is reported to be absorbed. Following oral administration, the apparent mean terminal elimination half-life of risperidone is 3 hours. Peak Plasma concentrations achieved after 1 to 2 hours of the oral administration.[4]

Review of Literature

The chapter 'Literature Review' contained the general concepts of mucoadhesive buccal drug delivery and its applications. Advantages and limitations of drug delivery through buccal mucosa were listed. Description of the oral cavity as a site for drug delivery was explained. Factors affecting oral mucosal drug delivery system and possible routes for drug transport across the oral mucosa were discussed. Advantages and disadvantages of drug delivery through buccal mucosa were listed. Different types of buccal dosage forms and important components of mucoadhesive buccal patches were explained. The processes for buccal absorption of drug, factors of the theories of bioadhesion, *in vitro* drug release methods and *in vivo* drug absorption methods were mentioned. Modern approaches of mucosal drug delivery systems were described. The processes for buccal absorption of drug, factors of the theories of

bioadhesion, *in vitro* drug release methods and *in vivo* drug absorption methods were mentioned. A detailed description about risperidone and polymer were discussed.

Methodology

In order to solve the objectives of this dissertation, suitable analytical method (UV Spectroscopy) was established and validated in 0.1 N hydrochloric acid and phosphate buffer (pH 6.6). Absorption of risperidone in buccal mucosa and buccal absorption tests in human volunteers were done using risperidone solution in phosphate buffer (pH 6.6). Physical parameters such as thickness uniformity, folding endurance, weight uniformity, content uniformity, swelling behaviour, percentage moisture loss, tensile strength, percentage elongation, and surface pH were carried out. In order to know the pattern of release of risperidone from patches, *in vitro* studies were done by static method in phosphate buffer pH 6.6. *In vivo* absorption studies in rabbits and human volunteers were performed to know the absorption pattern of risperidone from patches. *In vitro* and *in vivo* correlation of risperidone buccal patches was estimated. Short-term stability studies were conducted.

Results and Discussion

The results and discussion obtained from different methods of this thesis were described under different tables and graphs. Buccal absorption test for risperidone gave encouraging results to choose it as suitable drug for buccal drug delivery systems. *In vitro* release studies of risperidone buccal patches showed almost all the drug was released in 50 minutes. The release of risperidone followed zero order. The release mechanism of risperidone from buccal patches (II to V) was diffusion rate limited which was confirmed by Higuchi's model. Patch I followed dissolution rate controlled which was confirmed by Hixon-Crowell model. *In vivo* absorption of risperidone buccal patch studies revealed that adequate percent of drug was absorbed

within 30 min in case of rabbit and human volunteers. The absorption pattern followed first order. Good correlation was achieved among *in vitro* release and *in vivo* absorption studies.

Conclusions

The conclusions drawn from the present investigation are;

9) The buccal absorption test was conducted on human volunteers to verify the extent of absorption of risperidone through buccal route. About 26.10% of the administered dose (1 mg) of risperidone was absorbed in 5 min. The results were encouraging.
10) Mucoadhesive patches of risperidone containing 1 mg of drug were prepared successfully using HPMC (15 & 47cps), PVA, and ethyl cellulose polymers in different combinations and there were total seven films were prepared. Based on observations, six formulations were selected and used for further analysis. The films exhibited satisfactory characteristics regarding to integrity, flexibility, dispersion of drug, and other quality control parameters. Additives such as glycerin (plasticizer) and Tween-80 (dispersing agent) were included in the formulations.
11) The *in vitro* release of risperidone from the patches I to VI was in the range of 35.64 to 72.33% in 30 min, in phosphate buffer solution, pH 6.6. The release kinetics indicated zero order release from all the patches.
12) Higuchi's diffusion model and Hixon-Crowell cube root law were applied to test the release mechanism. R^2 values are higher for Higuchi's model compared to Hixon – Crowell model for all the patches. Hence risperidone release from the patches followed diffusion rate controlled.

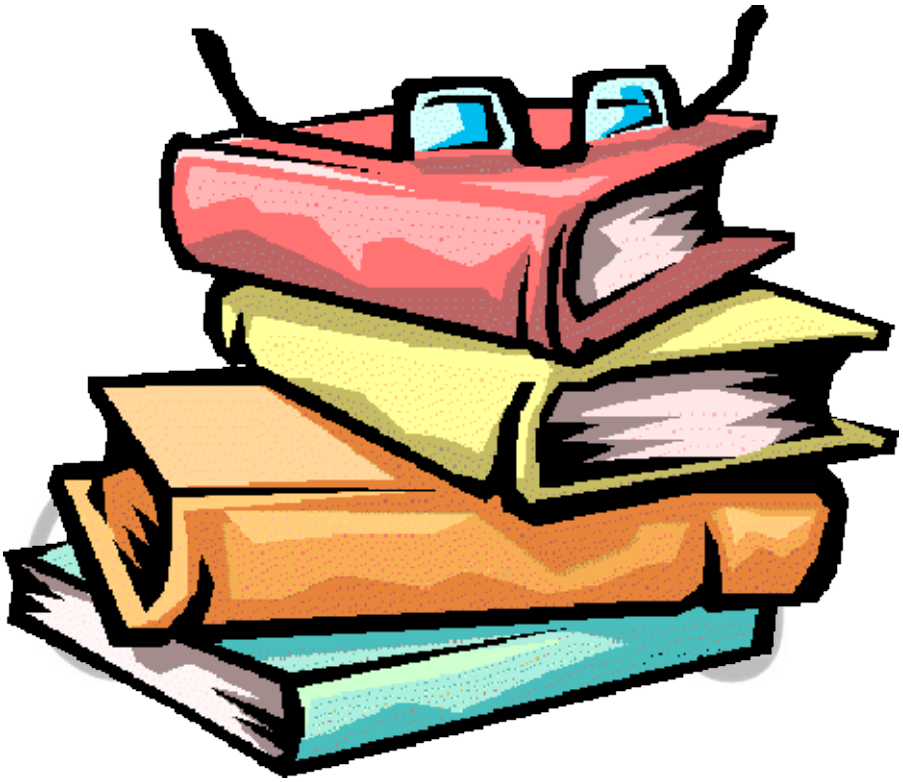
13) The *in vivo* buccal absorption kinetics in rabbits indicated that about 80.40% of the drug was absorbed in 30 min from the patch V. The absorption kinetics was studied by regression analysis (R^2 =0.999). The absorption of risperidone followed first order.

14) The *in vivo* buccal absorption kinetics in human volunteers indicated that about 80.78% of the drug was absorbed in 30 min from the patches. It indicates that the risperidone has an intrinsic ability to absorb from buccal mucosa. Drug absorption followed first order and is in tune with rabbits buccal absorption.

15) The *in vitro-in vivo* correlations (IVIVC) were attempted for the release and absorption of risperidone patches. The correlation coefficient for patch V was 0.996.

Thus, the objectives of the thesis are achieved.

Good results were obtained from *in vitro* and *in vivo* conditions for risperidone films. The buccal release of risperidone from patches in healthy human beings and rabbits showed a significant improvement. The results can be extrapolated to the human beings as the structure and permeability of buccal membrane of rabbits is similar to that of human beings. Hence the development of bioadhesive buccal formulations for risperidone may be a promising one as the dose of risperidone may be decreased and hence side effects may be reduced.



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