"DEVELOPMENT AND EVALUATION OF A BUCCAL DRUG DELIVERY SYSTEM FOR THE ANTI-ANGINAL DRUG-NICORANDIL"

Dissertation submitted to
The Tamil Nadu Dr. M.G.R. Medical University,
Chennai.

In partial fulfillment for the award of degree of
MASTER OF PHARMACY
(*Pharmaceutics*)

Submitted by
HONEY SUSAN PHILIP

Under the guidance of
Dr. K. Muthusamy, M. Pharm., Ph.D.,
Assistant Professor, Department of Pharmaceutics

MARCH 2010

COLLEGE OF PHARMACY
SRI RAMAKRISHNA INSTITUTE OF PARAMEDICAL SCIENCES
COIMBATORE – 641 044.

Certificate

This is to certify that the dissertation entitled ***"DEVELOPMENT AND EVALUATION OF A BUCCAL DRUG DELIVERY SYSTEM FOR THE ANTI-ANGINAL DRUG-NICORANDIL"*** *was carried out by* ***HONEY SUSAN PHILIP*** *in the Department of Pharmaceutics, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, which is affiliated to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, under my direct supervision and guidance to my fullest satisfaction.*

Dr. K. Muthusamy, M.Pharm., Ph. D.,
Assistant Professor,
Dept of Pharmaceutics,
College of Pharmacy
S.R.I.P.M.S.,
Coimbatore – 44

Place: Coimbatore
Date:

Certificate

*This is to certify that the dissertation entitled "**DEVELOPMENT AND EVALUATION OF A BUCCAL DRUG DELIVERY SYSTEM FOR THE ANTI-ANGINAL DRUG-NICORANDIL**" was carried out by **HONEY SUSAN PHILIP** in the Department of Pharmaceutics, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, which is affiliated to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, under direct guidance and supervision of **Dr.K.Muthusamy, M.Pharm., Ph.D.**, Asst. Professor, Department of Pharmaceutics, College of Pharmacy, SRIPMS, Coimbatore.*

Dr. M Gopal Rao, M.Pharm., Ph.D
Vice- Principal and Head,
Department of Pharmaceutics,
College of Pharmacy,
S.R.I.P.M.S.,
Coimbatore – 44

Place: Coimbatore
Date:

ACKNOWLEDGEMENT

It gives me immense pleasure in submitting my dissertation titled ***"DEVELOPMENT AND EVALUATION OF IMMEDIATE RELEASE TABLETS OF A BUCCAL DRUG DELIVERY SYSTEM FOR THE ANTI-ANGINAL DRUG-NICORANDIL."*** *. "No work is accomplished, with optimum refinement, support and indulgence of others"*

I take this opportunity with pride and immense pleasure in expressing my deep sense of gratitude to my guide ***Dr. K.Muthusamy, M.Pharm., Ph.D****, Asst.Professor, Department of Pharmaceutics, for his excellent suggestions, invaluable guidance, constant inspiration and sustained interest throughout my work.*

I also express my sincere gratitude and respect to ***Dr. M. Gopal Rao, M.Pharm., Ph.D.,*** *Vice Principal and Head, Department of Pharmaceutics for his continued encouragement, guidance and invaluable advice.,*

I wish to express my sincere thanks to our beloved Principal ***Dr.T.K. Ravi, M.Pharm., Ph.D., FAGE****, for his kind co-operation and encouragement and lending me all the facilities required to proceed with my study.*

I am very much thankful to ***Dr. Gandhimathi, M.Pharm. Ph.D,*** *Department of Pharmaceutical Analysis, for helping me to carryout the analytical and interpretation studies.*

I express my sincere thanks to ***Sai Mirra Innopharm Pvt Ltd*** *for providing me with the required drug to carry out this project..*

I would like to thank ***Mr. Ramakrishnan, M.Sc., B.Ed., (Ph.D.), Mr.S.Muruganandham, Ms. Geetha, Mrs. Kalaivani*** *and* ***Librarians*** *for their kind co-operation during this work.*

Words can't express my sincere gratitude and obligation to my dear batch mates ***ArunRaj, Divia, Daphne, Jyothi, Mounika, PhaniKrishna, Ranganathan, Santhosh, Swathi*** *who directly and indirectly helped me during my work.*

I owe a great debt of gratitude to my friend, ***Mr. G. Thanumalaiyan*** *for his invaluable cooperation and encouragement for the success of my work.*

I would like to thank my roommate ***Anju Gopi****, for her cooperation during my work.*

I bow to my affectionate, ***Mom Lilly*** *and* ***Dad Philip*** *for their precious love, affection, prayers and moral support which guided me in the right path and are also the backbone for all the successful endeavors in my life. I express my sincere gratitude to my* ***husband Jinesh Koshy*** *for his moral support and timely help in completing my thesis. I extent my love and gratitude to my* ***sister Sonia Philip*** *for her love and support throughout my life.*

I submit my sincere thanks to our managing trustee ***Sevaratna Dr.R Venkatesalu*** *for providing us all the facilities in this institution.*

I wish to thank of ***M/s. Computer Park*** *for framing project work in a beautiful manner.*

I wish to thank ***one and all*** *who were directly and indirectly responsible for the successful completion of the thesis.*

*Above all, I humbly submit my dissertation work, into the hands of the **Almighty**, who is the source of all wisdom and knowledge for the successful completion of my thesis.*

HONEY SUSAN PHILIP

LIST OF FIGURES

S.NO.	PARTICULARS	PG. NO.

LIST OF TABLES

1. INTRODUCTION

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinicians alike. However, peroral (Jain, 2003) administrations of drugs have disadvantages such as hepatic first-pass metabolism and enzymatic degradation within the GI, which that prohibits oral administration of certain classes of drugs.

Consequently, other absorptive mucosae are considered as potential sites for drug administration. Transmucosal routes of drug delivery (i.e., mucosal linings of the nasal, rectal).

- Buccal Delivery system
- Oral Delivery System
- Vaginal delivery system
- Rectal delivery system
- Nasal Delivery System
- Occular Delivery system

1.1 FUNDAMENTALS OF BIOADHESION

Development of an adhesive bond b/w a polymer and biological membrane or its coating can be visualized as a 2-step process. (Lenaerts *et al*., 1990).

- Step 1 – Initial contact b/w the 2 surfaces
- Step 2 – Formation of secondary bonds due to non-covalent interaction.

This process of bond formation attributed to surface of the biological membrane, surface of the adhesive and the interfacial layer between the two surfaces. Molecular events that take place in the interfacial layer depend on the properties of the polymer and membrane.

Bioadhesive polymers

Bioadhesive polymers are classified into 2 main categories.

1. Polymers that are water soluble, linear and random polymer
2. Water insoluble compounds that has swellable networks joined by cross-linking agents.

There are so many properties associated with bioadhesive property of polymers.

- Molecular weight, chain length and cross-linking density
- Charges and Ionization
- Hydrophilic group and hydration
- Chain segment mobility

1.2 MECHANISM OF BIOADHESION

Several theories of bioadhesion have been proposed to explain fundamental mechanisms of attachment (Deryaguin *et al*., 1997).

a. Electronic theory

The adhesive polymer and mucus typically have different electronic characteristics when there two surfaces come in contact, a double layer of electrical charges form of the interface and then

adhesion develops due to the attractive force from e Transfer across the electrical double layer.

b. Adsorption Theory

In the adsorption theory, a bioadhesive polymer adheres to mucus because of two surface forces such as Vander Waals' forces, hydrogen bonds or hydrophobic interactions (Kaelbe, 1997).

c. Wetting Theory

Wetting Theory is predominantly applicable to liquid bioadhesive systems and analyses adhesive and contact behavior in terms of the ability of a liquid or a paste to spread over a biological system.

The work of adhesion, 'Y' being defined as the energy per cm^2 released when an interface is formed. The work of adhesion is given by:

$Wa = Y_A + Y_B + Y_{AB}$

where A, B refers to biological membrane and the bioadhesive formulation, respectively.

d. Diffusion Theory

The essence of this theory is that chains of the adhesive and the substrate interpenetrate one another to a sufficient depth to create a semi permanent adhesive bond, the penetration rate depends on the diffusion coefficients of both interacting polymers and the diffusion coefficient is known to depend on molecular weight and cross

linking density. (Champion, 1975; Wake, 1978). In addition, segment mobility, flexibility of the bioadherive polymer, mucus glycoprotein and the expanded nature of both networks are important parameters that need to be considered. Drug delivery via the membrane of the oral cavity can be subdivided as follows:

1. **Sublingual delivery** – which is the administration of drug via the sublingual mucosae (The membrane of the ventral surface of the tongue and the floor of the mouth) to the systemic circulation.
2. **Buccal delivery** - which is the administration of drug via the buccal mucosa (the lining of the cheek) to the systemic circulation.
3. **Local delivery** – For the treatment of conditions of the oral cavity, principally for ulcers, fungal conditions periodontal disease.

1.3 ADVANTAGES OF BUCCAL DRUG DELIVERY SYSTEM

Drug administration via the oral mucosae offers several advantages, (Khanna *et al*., 1998).

1. Ease of administration
2. Termination of therapy is easy
3. Permit localization of the drug to the oral cavity for a prolonged period of time.
4. Can be administered to unconscious patients

5. Offers an excellent route for the systemic delivery of drugs with high first pass metabolism, thereby offering a greater bioavailability.
6. A significant reduction in dose can be achieved thereby reducing dose dependent side effects.
7. Drugs which are unstable in the acidic environment are destroyed by the enzymatic or alkaline environment of the intestines can be administered by this route.
8. Drugs which show poor bioavailability via the oral route can be administered conveniently.
9. It offers a passive system for drug absorption and does not require any activation.
10. The presence of saliva ensures relatively less amount of water for drug dissolution unlike in case of rectal and transdermal routes.
11. Systemic absorption is rapid.
12. This route provides an alternative for the administration of various hormones, narcotic analgesic, steroids, enzymes, cardiovascular agents, etc.
13. The buccal mucosa is highly perfused with blood vessels and offers a greater permeability than the skin.
14. It allows for the local modification of tissue permeability, inhibition of protease activity or reduction in immunogenic response. Thus, relative use of therapeutic agents like peptides, protein and ionized species can be achieved.

15. Therapeutic return concentration of the drug can be achieved more rapidly.

1.4 LIMITATIONS OF BUCCAL DRUG ADMINISTRATION

Drug administration via this route has certain limitations (Khanna *et al*., 1998)

1. Drug, which irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odor, cannot be administered by this route.
2. Drugs, which are unstable at buccal pH, cannot be administered by this route.
3. Only drugs with small dose requirements can be administered.
4. Drug contained in the swallowed saliva follows the peroral route and advantages of buccal route are lost.
5. Only those drugs, which are absorbed by passive diffusion, can be administered by this route.
6. Eating and drinking may become restricted
7. There is an ever present possibility of the patient swallowing the tablet.
8. Over hydration may lead to the formation of slippery surface and structural integrity of the formulation may get disrupted by this swelling and hydration of the bioadhesive polymers.

1.5 OVERVIEW OF THE ORAL MUCOSA

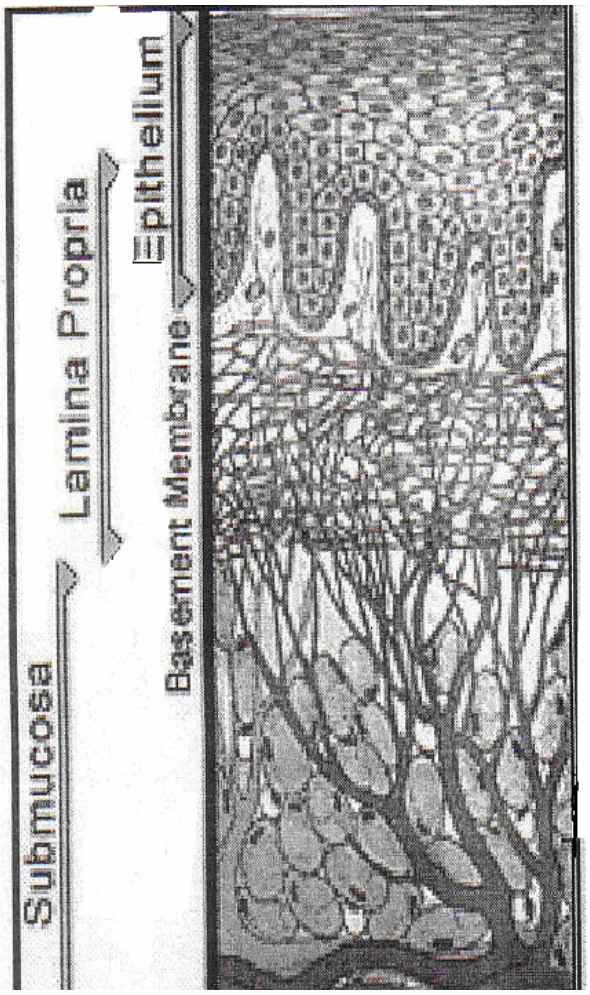


Fig 1. Cross section view of buccal mucosa

The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propia followed by the sub mucosa as the innermost layer. The epithelia is similar to stratified squamous epithelia, found in the east of the body in that it has a mitotically active based cell layer, advancing through a number of

differentiating intermediate layers to the superficial layers, were cells are shed from the surface of the epithelium. The epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers.

The oral mucosal thickness varies depending on the site, the buccal mucosa measures at 500-800 µm**,** while the mucosal thickness of the head and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measure at about 100 – 200 cm. The mucosae of areas subject to mechanical stress (the gingivae and hard palate) are keratinized similar to the epidermis. The mucosae of the soft palate, the sublingual and buccal regions, however, are not keratinized. (Harris and Robinson, 1992). Non-keratinized epithelia, such as the floor of the mouth and buccal epithelia do not contain acylceramides and only have small accounts of ceramide.

They also contain small amounts of neutral but polar lipids, mainly cholesterol sulphate and glucosyl ceramides. These epithelia have been found to be consideration permeable to water than keratinized epithelia. (Squier et al., 1991)

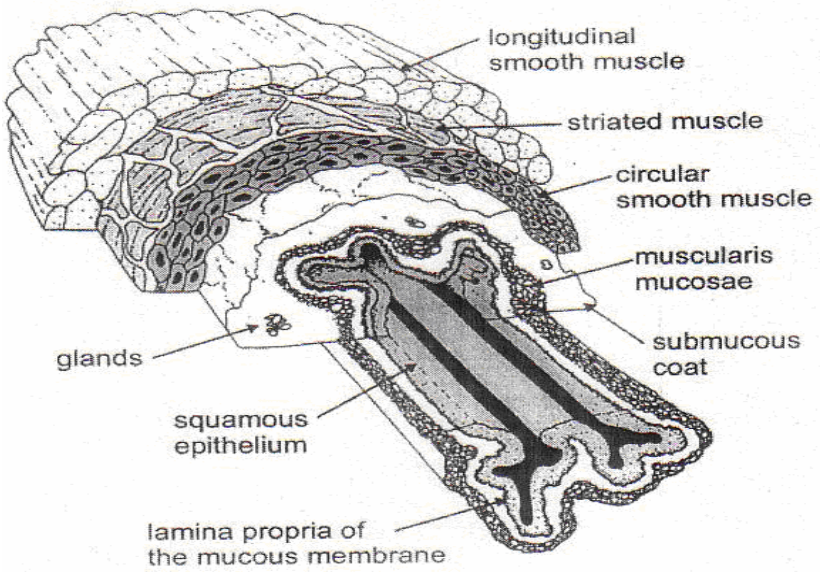


Fig-2. General structure of the oral mucosa

1.5 PERMEABILITY OF THE ORAL MUCOSA

There is considerable difference in permeability between different regions of the oral cavity. In general, the permeabilities of the oral mucosae decrease in the order: Sublingual > buccal > palatal. This rank order, however, is in accordance with the physical characteristics of these tissues, with the sublingual mucosae, being relatively thin, the buccal thicker and the palatal intermediate in thickness, but keratinized.

a. Mechanism of Transmucosal Permeation

The majority of drugs move across epithelial membranes, including the oral epithelia by passive mechanisms which are governed primarily by the laws of diffusion. (Martindale, 2002). In the case of simple diffusion, two potential routes of material transport across the epithelium are the ***Paracellular*** and

Trancellular pathways. The paracellular route involves the passage of molecules through intercellular space, while the transcellular route involves transport into and across the cells.

Substances with a high solubility in lipid are expected to traverse the oral mucosa more easily by moving along, across the lipid–rich plasma membranes of the epithelial cells, while water-soluble substances and ions probably more through the intercellular spaces.

Transmucosal permeation of polar molecules, such as peptide based pharmaceuticals, may be by way of paracellular route however, several barriers exist during the course of paracellular permeation.

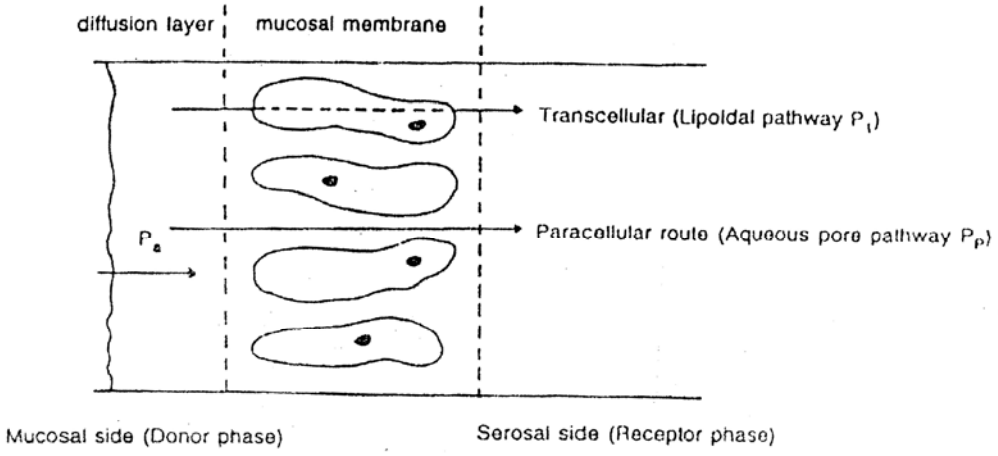


Fig-2a. Mechanism of Transmucosal permeation

b. Factors Important to Muccoadhesion

The bioadhesive power of a polymer or of a series of polymers is affected by the nature of the polymer and also the nature of the secondary media (Duchene *et al.*, 1988).

Polymer related factors

- Molecular Weight,
- Concentration of active polymers,
- Flexibility of polymer chains,
- Spatial conformation.

Environment related factors

- pH,
- Applied strength,
- Initial contact time,
- Selection of model substrate surface,
- Swelling.

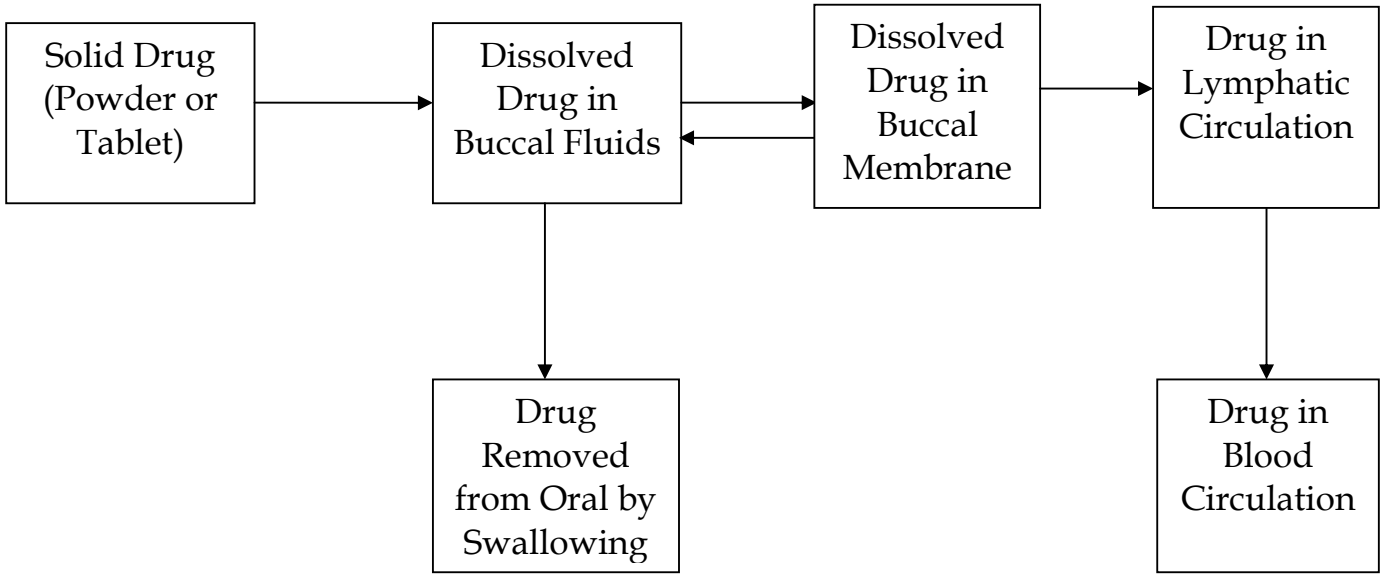


Fig-3. Schematic Representation of the Absorption kinetics of buccally administered drugs

c. Permeation Enhancers

Many compounds have been cited which are used as oral mucosal permeation enhancers (Shojari, 1998).

Table- 1. List of compounds used as oral permeation enhancers.

23-laury either	Cetylpyridinium chlocide
Apotion	Cetyl trimethylammonium bromide
Azone	Lysophosphatidylcholine
Benzalkonium chloride	Methyloleate
Cyclodentrin	Oleic acid
Dentran sulphate	Phosphatdyl choline
Lauic acid	Poly oxyethylene
Propylene glycol	Sodium EDTA
Menthol	Sodium glycocholate
Methoxy salicylate	Sodium glycodeoxy cholate
Polysorbate 80	Sodium tauryl sulphate
Sodium salicylate	Sodium taurodexycholate

d. Muccoadhesive Polymers

Mucoadhesive polymers can be differentiated based on their adhesive performance.

Table 2. Mucoadhesive polymers classified according to their adhesive performance

Excellent biohesives	Fair performing polymers	Poor agents
Carboxymethyl cellulose	Gum Karaya	Pectis
Carbopol 934	Gelatin	Polyvinyl pyrrolidone
Polycarbophil	Guar gum	Polyethylene glycol
Tragacanth		Psyllium
Poly acrylicacid		Amberlite - 200 resin
Sodium alginate		
Hydroxyethyl cellulose		

1.6 EXPERIMENTAL METHODOLOGY FOR BUCCAL PERMEATION STUDIES

Before a buccal drug delivery system can be formulated, buccal absorption/ permeation studies must be conducted to determine the feasibility of their route of administration, for the candidate drug. These studies involve methods that could examine *in vitro/in vivo* buccal permeation profile and absorption kinetics of the drug. (Shojari, 1998).

IN VITRO METHODS

For the *in vitro* studies, animals are sacrificed immediately before the start of an experiment. Buccal mucosa with underlying connective tissue is surgically removed from the oral cavity, the

connective tissue is then carefully removed and the buccal mucosal membrane is isolated. The membranes are then placed and stored in ice-cold (4ºC) buffers until mounted between side-by-side diffusion cells for the *in vitro* permeation experiments.

Dowfy *et al*, studied tissue viability by using ATP levels in rabbit buccal mucosae using ATP levels as an indicator for tissue viability is not necessarily an accurate measure however. Dowfy *et al*, reported a 50% drop in the tissue ATP concentration during the initial 6h of the experiment without a corresponding drop in tissue permeability.

If the drug permeability does not change during the time course of the study under the specific experimental conditions of pH and temperature, then the tissue is considered viable.

IN VIVO METHODS

Using this method, the kinetics of drug absorption was measured. The methodology involves the swirling of a 25 ml sample of the test solution for up to 15 minutes by human volunteers followed by the expulsion of the solution. The amount of drug remaining in the expelled volume is then determined in order to assess the amount of drug absorbed. The drawbacks of this method include salivary dilution of the drug, accidental swallowing of a portion of a sample solution, and the inability to localize the drug solution, within a specific site (buccal, sublingual or gingival) of the oral cavity.

A feasible approach to achieve absorption site localization is to retain the drug on the buccal mucosa using a bioadhesive system. Pharmacokinetic parameters such as bioavailability can then be calculated from the plasma concentration vs. time profile.

EXPERIMENTAL ANIMAL SPECIES

For *in vivo* investigations, many researches have used small animals including rats and hamsters for permeability studies. The rat has a buccal mucosa, with a very thick keratinized surface layer. The rabbit is the only lab rodent that has non-keratinized mucosal lining similar to human tissue has been extensively utilized in experimental studies. The oral mucosa of larger experimental animals that has been used for permeability and drug delivery studies include monkeys, dogs and pigs.

1.8 EVALUATION OF NICORANDIL-BUCCAL TABLETS

1. Weight variation test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance, and the test was performed according to the official method as in USP. The weight variation allowed as per USP limit is 7.5%. The weights of individual tablets were within the USP limits.

2. Drug content assay

The prepared buccal tablets containing Nicorandil was tested for drug content uniformity as per specifications of IP 1996. Five

tablets were weighed individually, and the drug was extracted in water. The drug content was determined as described. An accurately weighed amount of powdered nicorandil granules (100 mg) was extracted with water and the solution was filtered through 0.45-µ membrane (New Delhi, India). The absorbance was measured at 262 nm after suitable dilution.

3. Thickness and diameter

Uniform compression force and volume of die fill leads to uniform thickness. From each batch, 3 buccal tablets were taken and checked with a electronic thick-ness gauge (Mitutoyo, New Delhi, India). Similarly, three tablets were taken and checked for diameter using vernier.

4. Hardness

For each formulation, the hardness of 3 tablets were determined using the Monsanto hardness tester (Cad-mach, Ahmedabad, India), and the average was calculated.

5. Friability

For each formulation, the friability of 10 tablets were determined using the Roche friabilator (Camp-bell Electronics, Mumbai, India), respectively.

$$\% \text{ Friability} = \frac{\text{Loss of weight}}{\text{Initial weight}} \times 100$$

6. *In-vitro* drug release studies

The *in-vitro* dissolution studies were carried out using USP apparatus type II (Tab-Machines, Mumbai, India) at 75 rpm. The dissolution medium consisted for the phosphate buffer pH 6.8 (250 ml), maintained at 37°C ± 0.5°C. The formulated tablets containing Nicorandil equivalent to 3mg and 5mg were taken and kept in the dissolution medium and the paddle type stirrer was adjusted to 75 rpm. 5ml aliquot dissolution media was withdrawn at intervals and volume withdrawn was replaced with fresh quantity of dissolution media. The drug release at different time intervals (1h, 2h, 3h, 4h, 5h, 6h, 7h, and 8h) was measured by diode array UV-visible spectrophotometer at 262 nm.

The percentage of Nicorandil dissolved at various time intervals was calculated and plotted against time.

7. FT-IR compatibility studies

Weighed amount of the drug (3mg) was mixed thoroughly with 100mg of potassium bromide (dried at 40° -50° C) which was then compressed under 10 ton pressure in a hydraulic press to form a pellet which was then scanned from 4000 - 400^{-1}cm using FT-IR 410 PC spectrophotometer. The same procedure was repeated for polymers and formulations. The IR spectrum of nicorandil was compared with the IR spectrum of formulation.

8. Dissolution kinetics of drug release

The drug release data of nicorandil were fitted to models representing Zero order (cumulative amount of drug released vs time), First order (log cumulative percentage of drug remaining vs time), Higuchi's (cumulative percentage of drug released vs square root of time), and Korsmeyer's equation (log cumulative percentage of drug released vs log time) kinetics to know the release mechanisms. The data were processed for regression analysis using MS-EXCEL statistical functions. These data indicated that the drug release followed the diffusion controlled model as described by Higuchi's square root of time equation.

2. REVIEW OF LITERATURE

2.1 **Ashwin *et al.*, (2002)** studied the development and *in-vivo* evaluation of buccal tablets prepared using danazol-sulfobutyl ether 7 β– cyclodextrin (SB & 7) complexes. They developed a muccoadhesive controlled release formulation of danazol sulfobytyl ether 7 B-cyclodextrin complex with different types of polymers, such as polycarbophil (PC) and HPMC to evaluate the feasibility of improving the bioavailability of danazol via the buccal route. Increased mucoadhesion was observed for PC containing tablets compared with HPMC tablets. As the concentration of the polymer increased, drug release decreased and PC containing, tablets gave slower release compared to HPMC tablets.

2.2 **Paulo *et al.*, (2002)** studied on development of buccal formulations based on chitosan microspheres containing chlorhexidine diacetate. The micro particles were prepared by spray-drying technique, their morphological characteristics were studied by SEM and *in vitro* release behavior was investigated in pH 7.0 USP buffer.

2.3 **Shein *et al.*, (2000)** studied the enhanced bioavailability by buccal administration of triamicinolone acetonide from the bioadhesive gels in rabbits. The pharmacokinetics and bioavailability of triancinolone acetonide were determined to investigate buccal absorption from the mucoadhesive gels in rabbits. The entrancing affects of sodium deoxycholate as an enhancer on the buccal

absorption of triamcinolone acetonide from the mucoadhesion gels was evaluated in rabbits. Buccal administration of tramcinolone accetonide gels containing sodium deoxycholoate as an enhancer to rabbits showed a relatively constant, sustained blood concentration with minimal fluctuations.

2.4 **Wong *et al.*, (1999)** formulated and evaluated the controlled release buccal patches of Eudragit ME4OD, various bioadhesive polymers, namely HPMC, SCMC and carbopol of different grades, were incorporated into the patches, to modify their bioadhesive properties as well as the rate of drug release using metoprolol tartarate as model drug. The incorporation of hydrophilic polymers was found to affect the drug release as well as the rate of drug release using metoprolol tartarate as model drug. The incorporation of hydrophilic polymers was found to affect the drug release as well as enhance the bioadhesion. Although high viscosity can enhance the bioadhesions of the patches, they also tend to cause non-homogenous distribution of polymers and drug resulting in non-predictable deep release rates.

2.5 **Michel *et al.*, (1987)** carried out preliminary studies of oral mucosal delivery of peptide deeps. Comparison of plasma levels from buccal delivery verses i. v. infusion concluded that the buccal route has substantial potential for administration of peptides.

2.6 Hemant *et al.,* (1999) carried out study to evaluate the gum Hakea as a sustained released and muccoadhesive component in buccal tablets following their application to the buccal mucosa of rabbits. Results concluded that the gum Hakea may not only used to sustain the release of chlorpheniramine maleate from buccal tablets but also demonstrate that the tablets are sufficient mucoadhesive for clinical application.

2.7 Hessel *et al.,* (1989) carried cut comparison b/w bioavailability of prochlorperazine by IM, peroral and buccal routes. Final result concluded that elimination half-life was the least, with the buccal route and steady state plasma levels could be achieved using only 60% of the oral dose on buccal administration.

2.8 **Sathish and Vincent, (1986**) carried out study with respect to enkephelin hydrolysis in homogenates of various absorptive mucosae of the albino rabbit in order to assess similarities in rates and involvement of amino peptidases. Results concluded that the same enzymatic barrier to en kephalin absorption possibility exists in both the oral and non-oral mucosae.

2.9 **Aungst *et al.,* (1988)** (carried out study with respect to comparison of the effects of various transmucosal absorption promoters on buccal insulin delivery. Results concluded that non-ionic surfactants wherein the hydrophobic and hydrophilic portions are joined through ether linkage can be effective buccal absorption promoters but that those with other bonds are not.

2.10 **Laila *et al.*, (1992)** carried out study with respect to buccal absorption of Ketobemide and various ester prodrugs in the rat. Results concluded that all prodrugs show an increased extend of absorption relative to that of the parent drug.

2.11 **Patel *et al.*, (2006)** prepared buccal adhesive patches containing 20 mg of propanolol hydrochloride using solvent casting method. Patches were prepared at different ratios of PVP K-30 which generally enhances the releasing rate and evaluated for various physicochemical characteristics such as weight variation, drug content conformity, folding endurance, surface pH, mucoadhesive strength, *ex-vivo* residence time, in vitro drug release and *in vitro* buccal permeation study. Patches exhibited sustained release over a period of 7 hours. The mechanism of drug release was found to be non-ficikian diffusion.

2.12 **Nina *et al.*, (2005)** studied the enhanced bioavailability by buccal adminstration of PACAP (Pituitary adenylate cyclase – activating polypeptide). A strong mucoadhesive chetosaric-thiogloycolic acid (TG A) conjugate in combination with reduced glutathione (GSH) on permeation of PACAP across buccal mucosa were used. Release studies indicated that a controlled release can be provided from tablets consisting of chitosan – TGA at a pH of 5, whereas more than twice as much was released from chitosan TGA tablets pH4. Combination of permeation enhancing properties, controlled drug release and muccoadhesion character, chitosan –

TGA conjugates represent a promising tool for buccal administration of PACAP.

2.13 **Reinhold *et al.*, (1989)** developed and evaluated buccoadhesive patches, consisting of two ply laminates of an impermeable backing layer and a hydrocolloid polymer layer containing the drug. Patches were prepared by a casting procedure using various aqueous solutions of drugs and hydrocolloid polymers and subsequent drying. The polymers used were hydroxyl ethyl cellulose, hydroxyl propyl cellulose, polyvinyl pyrollidone and polyvinyl alcohol. Adhesion to the mucosal surface was established by interactions of the swollen polymer and buccal mucosal layer. A wide range of controlled drug release rate can be achieved by polymer dissolution kinetics.

2.14 Smart *et al.*, (1991) developed an *in vitro* method for assessment of the adhesive force between a disc of test material and a model mucus membrane and the method has reproducibility. It was concluded that only a small force is required to retain a dosage form within the buccal cavity. Carbopol 934P and EX55 (Polycarbophil) formed the most stable adhesive bond which remained intact for 8 hours.

2.15 **Carmen *et al.*, (1998)** prepared buccal bilayered device containing mucoadhesive and drug free backing layer by two different methods namely by a casting/solvent evaporation technique and bilayered tablets were obtained by direct compression. The mucoadhesive layer composed of a mixture of drug (Nifedipine or

Propanolol Hydrochloride) and chitosan with or without an anionic crosslinking polymer (polycarbophil, sodium alginate, gellan gum) and backing layer made of ethylcellulose. Bilaminated film showed sustained release in pH 6.4 phosphate buffer. Uncrosslinked chitosan containing device absorbed large quantity of water gel and eroded allowing drug release. Crosslinked chitosan with carbophil displayed controlled release and adequate adhesivity.

2.16 **Han-Gon *et al.*, (2000)** developed an omeprazole buccal adhesive tablet. A mixture of sodium alginate and HPMC was selected as the bioadhesive additive for the omeprazole tablet. The bioadhesive polymers alone had the bioadhesive force suitable for buccal adhesive tablets, but the suitability in human saliva was not satisfied. So magnesium oxide is used as an alkali stabilizer, due to its waterproofing effects. It was concluded that two tablets composed of (omeprazole/ sodium alginate/HPMC/Magnesium oxide [20/24/6/50.mg/tab] and [20/30/0/50 mg/tab] could be attached to human cheeks without collapse and could be stabilized in human saliva for atleast 4 hours.

2.17 **Juan Manuel *et al.*, (2002)** designed a two layered mucoadhesive tablet containing nystatin for the treatment of oral candidosis. Lactose CD, Carbomer (CR), hydroxyl propyl methyl cellulose (HPMC) was used as excipients. Properties such as *in vitro* mucoadhesion, water uptake, front movements and drug release were evaluated. The mixture CB: HPMC, 9:1 showed good *in vitro*

mucoadhesion. A swelling –diffusion process modulates the release of nystatin from this layer. A non-fickian kinetic was observed.

2.18 **Varshosaz and Dehgahan, (2002)** prepared buccoadhesive controlled release tablets. The tablet contained 30mg of nifedipine and various amount of carboxymethylcellulose (CMC), carbomer (CP), polyvinylpyrolidone (PVP), polyvinyl alcohol (PVA), hydroxy propyl methyl cellulose (HPMC). The highest adhesion force was observed in 8:2 ratio of CP: CMC and 35%CP adhered for over 8 hours to the upper gum of 6 healthy human volunteer and a good correlation (r^2=0.989) was observed between drug released *in vitro* and *in vivo.*

2.19 **Desai and Kumar, (2004)** evaluated the mechanism of absorption of propanolol hydrochloride through porcine buccal mucosa. The tablet was prepared in a specially designed and fabricated punch. HPMC and Carbopol 934P were used as polymers. The tablets were evaluated for weight uniformity, friability, hardness, swelling, mucoadhesive strength, *in vitro* drug release, stability and *in vitro* acceptability. The order of release was by non – fickian diffusion and first order kinetics. *In vivo* studies indicated that tablet was comfortable in oral cavity, not heavy and did not cause any side effects.

2.20 **Ikinci *et al*., (2004)** developed a bioadhesive buccal tablet for delivery of nicotine. The bioadhesive polymers, carbomer (Carbopol 974P NF) and alginic acid sodium salt (NaAlg) were used in

combination with HPMC at different ratios. Magnesium carbonate was added as a pH increasing agent, *in vitro* studies and bioadhesion studies were carried out and found that they released nicotine for 8 hours period and remained intact except for the formulation containing CP: HPMC at 20:80 ratio.

2.21 Kashappa *et al*., (2004) prepared and evaluated a novel buccal adhesive system (NABS) containing propanolol hydrochloride using hydroxy propyl methyl cellulose (HPMC), Carbopol 934P. A special punch was fabricated and used while preparing an NBAS.NBAS was evaluated by weight uniformity, thickness, hardness, friability, swelling, mucoadhesive strength, *in vitro* drug release, and *in vivo* human acceptability studies. It was concluded that NBAS is superior, novel system that overcomes the draw back associated with the conventional buccal adhesive tablet.

2.22 Park and Munday, (2004) evaluated some naturally occurring bioincompatible materials such as xanthan gum, karaya gum, guar gum and glycol chitosan as mucoadhesive controlled release excipients for buccal drug delivery. Tablets were prepared in a range of 0-50% of gum, in which glycol, chitosan produced the strongest adhesion, but concentration greater than 50% w/w are required to produce a non-erodible matrix that can release for over 4 hours and swelling properties of tablets were found to know the ability of the material to produce sustained release.

2.23 **Vijayaraghavan and Ravi, (2004)** studied the effect of formulation variables on the buccal absorption of a low dose of nifedipine (ND) which was done firstly to determine the influence of the incorporation of natural flax seed polymer (FSP) on bioavailability of ND after peroral administration with buccal administration. Formulation contains 10mg of ND and 10, 20, 30, 40mg of FSP as well as peroral administration with buccal of a formulation of 10mg of ND alone. *In vitro* study carried out in pH (6.8) phosphate buffer and bioavailability studies were carried out in 9 male healthy volunteer. A HPLC method was used to determine the plasma concentration. Bioavailability was improved with 10mg and 30mg of FSP than ND alone. The inclusion of flax seed polymer into the formulation resulted in increase in bioavailability due to increase in adhesion and faster release characteristic of the polymer.

2.24 **Jamakandi *et al.*, (2009)** investigation aimed at evaluating the possibility of using different polymeric grades of hydroxypropyl methyl cellulose for the development of transdermal drug delivery systems of nicorandil, an anti-anginal drug. Prepared matrix-type patches were evaluated their physiochemical characterization followed by *in vitro* evaluation. Selected formulations were subjected for their *ex vivo* studies on porcine ear skin.

2.25 **Bupinder *et al.*, (2006)** designed oral controlled release mucoadhesive compressed hydrophilic matrices of atenolol. Tablets were prepared by direct compression and evaluated for bioadhesive strength and *in vitro* dissolution parameters. Carbopol 934P and

sodium carboxy methyl cellulose were taken as the independent variables. Compressed matrices exhibited non-Fickian drug release kinetics approaching zero order.

2.26 Shaila Lewis *et al.*, (2006) formulated mucoadhesive tablets for buccal administration of nicotine. Three types of tablets were developed each containing two mucoadhesive components (HPMC and Sodium Alginate), (HPMC and Carbopol), (Chitosan and Sodium Alginate). For each of these types, batches were produced changing the quantity of polymers resulting in nine different formulations. The tablets were evaluated for release pattern and mucoadhesive performance. Pharmacokinetic studies were conducted in smokers. A peak plasma concentration of 16.78±2.27 mg was obtained in two hours, which suggests potential clinical utility in Nicotine replacement therapy.

3. SCOPE AND OBJECTIVE OF THE WORK

The scope of any formulation primarily focuses on safety and efficacy of the drug delivery system. Now the focus has been slightly moved to the patient's convenience and acceptance, where still the safety and efficacy remain integrated with design. Recent research efforts through out the world have resulted in significant development of novel drug delivery systems.

In recent years, there has been increasing interest in the use of bioadhesive polymers to control the delivery of biologically active agents systemically or locally. These bioadhesive systems are useful for the administrative of drugs, which are susceptible to extensive gastro intestinal degradation and first pass metabolism. Bucolic adhesive system appears to be attractive because it avoids significant limitations of traditional routes of drug administration such as poor absorption, enzymatic degradation and first pass metabolism.

Buccal delivery necessitates the use of mucoadhesive polymer as their dosage forms should ideally adhere to the mucosa and withstands salivation, tongue movement and swallowing for a significant period of time.

The objective of the present study was to formulate a suitable drug delivery system through the buccal mode, for the long term treatment and prevention of angina pectoris.

Hypertension and angina pectoris, the most common cardiovascular diseases, require constant monitoring. The first therapeutic drug shown to possess an ability to hyperpolarize smooth muscle cell membranes is nicorandil, a potent coronary vasodilator **(**Frydman *et al*., 1989). Although nicorandil is one of the emerging molecules is the case of hypertension and angina, successful treatment means maintenance of blood pressure at a normal physiological level, for which a constant and uniform supply of drug is desired (Leonetti *et al*, 1989, Camm *et al*, 1989).

Buccal delivery of drugs provide an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of administration problems such as high first pass metabolism, drug degradation in harsh gastrointestinal environment can be circumvented by administering a drug via buccal route.

Moreover, buccal drug delivery offers a safer method of drug utilization, since drug absorption can be promptly terminated in case of toxicity by removing the dosage form the buccal cavity (Wong FC *et al*., 1999)**.** It is also possible to administer the drug to patients, who cannot be dosed orally to prevent accidental swallowing.

Buccal releases of nicorandil is enabled so that it can be retained in the oral cavity for desired duration and localize the dosage form in a specific region and control the release rate of drug.

4. PLAN OF THE WORK

The work entitled, "**DEVELOPMENT AND EVALUATION OF A BUCCAL DRUG DELIVERY SYSTEM FOR THE ANTI-ANGINAL DRUG-NICORANDIL**" was planned in an aim to achieve the objective described earlier. The work was carried out for a period of 9 months (May 2009 to January 2010) which was divided into three phases like

Phase I (May - June 2009)

1. Literature survey.
2. Identification of the objective for the current study.
3. Optimization of the methodology

Phase II (July - December 2009)

1. Preparation of standard graph for the drug.
2. Preparation of nicorandil buccal tablets by direct compression method.

    - Method 1- Buccal tablet with coated backing layer of ethyl cellulose.
    - Method 2- Bilayered buccal tablet with backing layer of ethyl cellulose.

3. Evaluation of the physical characteristics.

   3.1. Compatibility study using Infra Red (IR) spectroscopy.

   3.2. Tablet assessed with respect to physical parameters such as friability studies, FT-IR Studies, Swelling studies and swelling Index, tablet thickness, weight variation test, hardness and *n-vitro* drug release.

4. Drug content analysis.

5. Dissolution Kinetics of drug.

Phase III (January 2010)

1. Compilation and preparation of reports.

5. MATERIALS AND EQUIPMENTS

Table: 3 Materials used

Name of the materials	Name of the company
Nicorandil (gift sample)	Sai Mirra Innopharm Pvt Ltd, Chennai.
Carbopol 934	Hi Media Laboratories Ltd, Mumbai.
Polyvinyl alcohol	S.D.Fine Chemicals Ltd, Mumbai
Polyvinyl pyrollidone	S.D.Fine Chemicals Ltd, Mumbai
Ethyl Cellulose	Loba Chemie Pvt Ltd, Mumbai
Magnesium Stearate	Loba Chemie Pvt Ltd, Mumbai
Mannitol	S.D.Fine Chemicals Ltd, Mumbai
β-Cyclodextrin	S.D. Fine Chemicals Ltd, Mumbai
Distilled Water	Industrial Scientific Enterprises, Namakkal.

Table: 4. Equipments used

Name of equipment	Name of the company
UV / Vis Spectrophotometer	JASCO V-530.
Dissolution apparatus	Electrolab TDT-08L. Chennai.
Digital balance	Denver instruments
FT-IR Spectrophotometer	Jasco-FT-IR 8201 PC
Electronic Digital Micrometer	Aerospace Pvt. Ltd
Monsanto Hardness Tester	Cad-Mach, Ahmedabad, India
pH tester 1 (water proof)	Oakton instruments.

6. DRUG PROFILE

Nicorandil

Nicorandil is one of the emerging molecules in the case of hypertension and angina and behaves as a potent coronary vasodilator.

Chemical name

2-[(pyridin-3-ylcarbonyl) amino] ethyl nitrate

Empirical formula

$C_8H_9N_3O_4$

Chemical Structure:

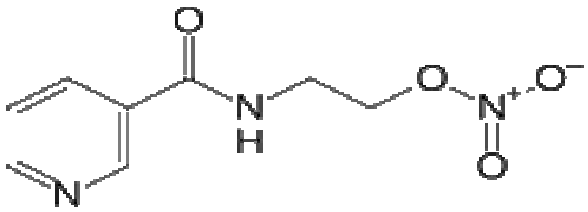


Fig : 4. Structure of Nicorandil

Mol. mass

211.175 g/mol

Characteristics

White or almost white powder. Freely soluble in water, acetone and chloroform.

6.1 PHARMACOLOGY

Nicorandil, a drug approved for the treatment of ischemic heart disease, has dual properties. The intrinsic mechanism of the drug (selective activation of K^+_{ATP}channels at the sarcolemmal and mitochondrial level) allows coronary and peripheral vasodilatation with subsequent reduction of preload and afterload. Secondly, because of the role K^+_{ATP}channels in ischemic preconditioning, nicorandil have been attributed cardio protective effects.

Nicorandil acts by relaxing the smooth muscle of the blood vessels, especially those of the venous system. It does this through two methods. Firstly, by activating potassium channels, and secondly by donating nitric oxide to activate the enzyme guanylate cyclase. Guanylate cyclase causes activation of GMP leading to both arterial and venous vasodilatation. As it is selective for vascular potassium channels, it has no significant action on cardiac contractility and conduction.

Although it can dilate the coronary vessels of a healthy individual, its effects on the coronary vessels of someone with ischaemic heart disease will be little as they will already be completely dilated. As it couples arterial dilation along with venodilation, it reduces the preload and the afterload of the heart.

6.2 INDICATIONS

- Angina Pectoris,
- Hypertension,
- Congestive heart failure

6.3 PHARMACOKINETICS

- Onset of Action -30min - 60 min
- Cmax -90 min
- Protein binding- 20-25%
- Metabolism –denitration of the molecule into the nicotinamide pathway,
- Elimination Half-life-2 hours

6.4 SIDE EFFECTS

Common side effects include flushing, palpitation, weakness, headache, mouth ulcers, nausea and vomiting. More recently peri-anal, ileal and peri-stomal ulceration has been reported as a side effect. Anal ulceration is now included in the British National Formulary as a reported side effect.

6.5 STABILITY

Store below 25°C. Protect from light and moisture.

6.6 CONTRAINDICATIONS AND PRECAUTIONS

Contraindications

Nicorandil is contraindicated in patients with cardiogenic shock, left ventricular failure with low filling pressures and in hypotension. It is also contraindicated in patients who have

demonstrated an idiosyncratic response or hypersensitivity to nicorandil. Due to the risk of severe hypotension, the concomitant use of Ikorel and phosphodiesterase 5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) is contraindicated.

Pregnancy implications

Animal studies have not shown drug related teratogenic or primary embryo toxic effects on animal fetuses; however comparative studies have not been done in humans. Use only when benefit outweighs potential risk in a pregnant woman.

6.7 DRUG INTERACTIONS

Drug –drug combinations

No pharmacological or pharmacokinetic interactions have been observed in humans or animals with beta-blockers, digoxin, rifampicin, cimetidine, acenocoumarol, a calcium antagonist or a combination of digoxin and furosemide. Nevertheless, there is the possibility that nicorandil may potentiate the hypotensive effects of other vasodilators, tricyclic antidepressants or alcohol.

Gastrointestinal perforations in the context of concomitant use of nicorandil and corticosteroids have been reported. Caution is advised when concomitant use is considered.

6.8 MARKETED FORMULATION

Table: 5 List of some marketed formulations of Nicorandil

Trade name	Tablet	Injection	Manufacturer
AV-COR	5mg,10mg		GRANDIX
CORFLO	5mg,10mg		WOCKHARDT
KORANDIL	5mg,10mg		SUN
NIKORAN	5mg,10mg	2mg, 4mg vials	TORRENT
ZYNICOR	5mg		ZYDUS CADILA

6.9 ADVERSE DRUG REACTIONS

The following undesirable effects have been reported from the original clinical trials for the prevention and long-term treatment of chronic stable angina and post-marketing experience. Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports.

Table: 6 List of some Reported Adverse Drug Reactions

SOC	FREQUENCY	ADR
Immune system disorders	Very rare	Angioedema
Nervous system disorders	Very common	Headache, usually of a transitory nature, especially when treatment is initiated
	Common	Dizziness
Cardiac disorders	Uncommon	An increase in heart rate at high doses
Vascular disorders	Common	Cutaneous vasodilation with flushing
	Uncommon	Hypotension at high therapeutic doses
Gastrointestinal disorders	Common	Nausea and vomiting
	Rare	Persistent aphtosis or mouth ulcers which were occasionally severe
Hepato-biliary disorders	Rare	Hepatic function abnormalities
Skin and subcutaneous tissue disorders	Rare	Various types of rash
Musculoskeletal & connective tissue disorders	Rare	Myalgia

7. POLYMER PROFILE

7.1 CARBOPOL-934

Chemical name	:	Acrylic acid copolymer
IUPAC name	:	prop-2-enoic acid
Chemical formula	:	$C_3H_4O_2$
Appearance	:	White, fluffy powder
Odor	:	Slightly acetic

7.1.1 Characteristics and application:

Maintain stability of the o/w type emulsion system, Applicable to various gel and cream, emulsion. Carbopol 934 is a superior suspending agent, which permits uniform and permanent dispersion of water-insoluble test compounds. Carbopol polymers have an average equivalent weight of 76 per carboxyl group. The general structure can be illustrated with fig.4 &5.

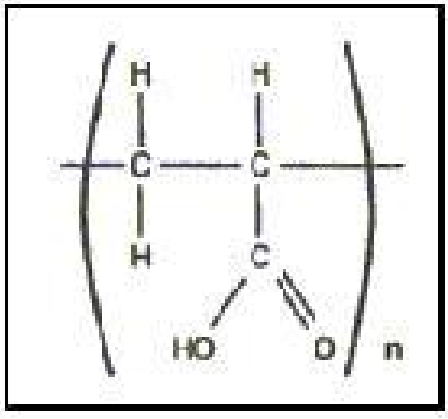


Fig : 4 Chemical Structure of Carbopol

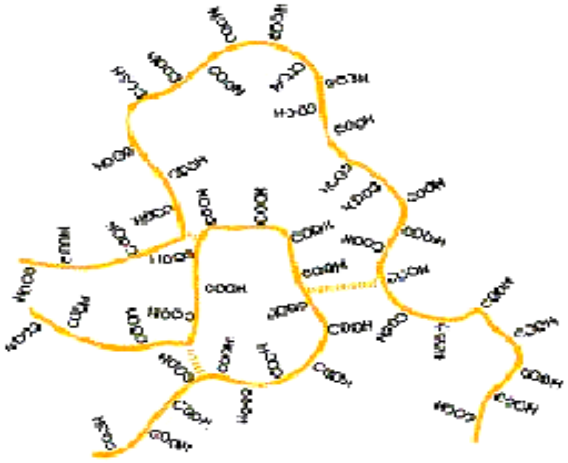


Fig : 5. General structure of carbopol polymers

7.1.2 Physical properties

Carbopol 934 P is cross-linked with allyl sucrose and is polymerized in solvent benzene. The three dimensional nature of these polymers confers some unique characteristics, such as biological inertness, not found in similar linear polymers. The Carbopol resins are hydrophilic substances that are not soluble in water. Rather, these polymers swell when dispersed in water forming a colloidal, mucilage-like dispersion.

Carbopol polymers are bearing very good water sorption property. They swell in water up to 1000 times their original volume and 10 times their original diameter to form a gel when exposed to a pH environment above 4.0 to 6.0. Because the pKa of these polymers is 6.0 to 6.5, the carboxylate moiety on the polymer backbone ionizes, resulting in repulsion between the native charges,

which adds to the swelling of the polymer. The glass transition temperature of Carbopol polymers is 105°C (221°F) in powder form. However, glass transition temperature decreases significantly as the polymer comes into contact of water. The polymer chains start gyrating and radius of gyration becomes increasingly larger. Macroscopically, this phenomenon manifests itself as swelling.

Appearance__ Fluffy, white, mildly acidic polymer

7.1.3 Rheological properties

While the relationships between structure and properties have been of interest both academically and in industry. Different grades of Carbopol polymers exhibit different rheological properties, a reflection of the particle size, molecular weight between crosslinks (Mc), distributions of the Mc, and the fraction of the total units, which occur as terminal, i.e. free chain ends.

The molecular weights between adjacent crosslinks (Mc) are approximately inversely proportional to the crosslinker density. These may be calculated from the functionality of the crosslinking monomer, the relative ratio of acrylic acid to crosslinking monomer, and the efficiency of the crosslinking reaction, assuming negligible chain ends. Alternatively, the molecular weight can be qualitatively compared to the rheological properties of a swollen gel and/or from the equilibrium-swelling ratio. In simple terms, low viscosity, low rigidity polymers, such as Carbopol 941 and Carbopol 971P, have a higher Mc. Conversely, they have lower crosslinker densities. The higher the crosslinker level, the lower the equilibrium swelling ratio.

7.1.4 Applications of carbopol polymers:

The readily water-swellable Carbopol polymers are used in a diverse range of pharmaceutical applications to provide:

- Controlled release in tablets.
- Bioadhesion in buccal, ophthalmic, intestinal, nasal, vaginal and rectal applications.
- Thickening at very low concentrations to produce a wide range of viscosities and flow properties in topical, lotions, creams and gels, oral suspensions and transdermal gel reservoirs.
- Permanent suspensions of insoluble ingredients in oral suspensions and topicals.
- Emulsifying topical oil-in-water systems permanently, even at elevated temperatures, with essentially no need for irritating surfactants.

Several properties of Carbopol make it potentially valuable as a pharmaceutical excipient in numerous applications such as:

7.1.5 Controlled release & solid dosage forms

Carbopol is being used in the controlled release solid dosage formulations since last four decades. Tablet formulations using Carbopol polymers have demonstrated zero-order and near zero-order release kinetics. These polymers are effective at low concentrations (less than 10%). Still they show extremely rapid and efficient swelling characteristics in both simulated gastric fluid

(SGF) and simulated intestinal fluid (SIF). The Carbopol polymers produce tablets of excellent hardness and low friability. These polymers can be successfully formulated into a variety of different tablet forms, including the traditional swallowable tablets, chewable tablets, buccal tablets, sublingual tablets, effervescent tablets, and suppositories; providing controlled-release properties as well as good binding characteristics. Carbomers show larger dissolution times at lower concentrations of the polymer.

Because of these factors Carbopol polymers have greater extent in formulating dosage forms. Because Carbopol polymers swell rapidly in water quantities and absorb great, to avoid the use of flammable solvents, roller compaction is being used as the method to prepare a new form of Carbopol polymer71 GNF. Carbopol polymer 71G NF is a useful and versatile controlled-release additive for tablet formulations in direct compression.

Drug dissolution mechanism from carbopol polymers

In the dry state, the drug is trapped in a glassy core. As the external surface of the tablet is hydrated, it also forms a gelatinous layer upon hydration; however, this gel layer is significantly different structurally from the traditional matrix tablet. The hydrogels are not entangled chains of polymer, but discrete microgels made up of many polymer particles, in which the drug is dispersed. The crosslink network enables the entrapment of drugs in the hydrogel domains. Since these hydrogels are not water soluble, they do not dissolve, and erosion in the manner of linear polymers

does not occur. Rather, when the hydrogel is fully hydrated, osmotic pressure from within works to break up the structure, essentially by sloughing off discrete pieces of the hydrogel. It is postulated that as the concentration of the drug becomes high within the gel matrix and its thermodynamic activity or chemical potential increases, the gel layer around the tablet core actually acts almost like a rate-controlling membrane, resulting in linear release of the drug. Because of this structure, drug dissolution rates are affected by subtle differences in rates of hydration and swelling of the individual polymer hydrogels, which are dependent on the molecular structure of the polymers, including crosslink density, chain entanglement, and crystalline of the polymer matrix. The magnitude and rate of swelling is also dependent on the pH of the dissolution medium. The channels which form between the polymer hydrogels are influenced by the concentration of the polymer, as well as the degree of swelling. Increasing the amount of polymer will decrease the size of the channels, as does an increase in swelling degree. All of these factors must be taken into account to describe the mechanism for release control in tablets formulated with Carbopol polymers.

Benefits in solid dosage application

- Efficient controlled release agents for matrix tablets.
- Improve bioavailability of certain drugs
- Efficient binders in dry as well as wet granulation processes.
- Only granular polymer (Carbopol 71G NF) available for direct compression formulation.

7.1.6 Oral suspension applications

For many years, Carbopol polymers have been widely used in oral suspensions to thicken, modify flow properties, suspend insoluble ingredients and provide bioadhesion. The significance of these polymers is that they eliminate the settling problem even at low concentrations. As Carbopol polymers swell when hydrated and neutralized, they form colloidal dispersion.

Carbopol 934 P has been used since mid 1960s. Carbopol 974 P has similar rheological properties to Carbopol 934 P, as both are highly cross-linked polymers that produce mucilage with very short flow rheology. Carbopol 971 P provides very low viscosities and excellent yield values at low usage levels. Suspensions formed with Carbopol 971 P will have longer rheology. Carbopol 71 G polymers will give same viscosities and rheology as Carbopol 971 P, but it is easier to handle and disperse due to its granular nature.

Benefits in oral suspension applications

- Long Term Stability of Suspensions over a wide pH range.
- Highly efficient at low use level.
- Taste masking of some bitter drugs.
- Build viscosity and yield value for “non-spill” pediatric formulations.

7.1.7 Bioadhesive applications

Bioadhesion is a surface phenomena in which a material may be of natural or synthetic origin, adheres or stick to biological

surface, usually mucus membrane. The concept of bioadhesion is emerging as a potential application in drug delivery due to its applicability for bioavailability enhancement, prolongation of residence time for drug in GIT and better contact between drug and absorbing surface.

Many hydrophilic polymers adhere to mucosal surfaces as they attract water from the mucus gel layer adherent to the epithelial surface. This is the simplest mechanism of adhesion and has been defined as "adhesion by hydration" Various kinds of adhesive force, e.g. hydrogen bonding between the adherent polymer and the substrate, i.e. mucus, are involved in mucoadhesion at the molecular level. Carbopol polymers have been demonstrated to create a tenacious bond with the mucus membrane resulting in strong bioadhesion.

Many commercial oral and topical products available today and under investigation have been formulated with Carbopol polymers, as they provide numerous benefits in bioadhesive formulations.

Benefits in bioadhesive applications

- Improve bioavailability of certain drugs.
- Enhance patient compliance (fewer doses are needed per day)
- Lower concentrations of the active ingredients can be used.
- Provide excellent adhesion forces.

7.1.8 Topical applications:

Carbomers are very well suited to aqueous formulations of the topical dosage forms:

- **Safe & Effective** : Carbopol polymers have a long history of safe and effective use in topical gels, creams, lotions, and ointments. They are also supported by extensive toxicology studies
- **Non-Sensitizing** : Carbopol polymers have been shown to have extremely low irritancy properties and are non-sensitizing with repeat usage.
- **No Effect on the biological activity of the drug**: Carbopol polymers provide an excellent vehicle for drug delivery. Due to their extremely high molecular weight, they cannot penetrate the skin or affect the activity of the drug.
- Excellent **thickening, suspending, & emulsification** properties for topical formulations

7.1.9 Oral care applications

Carbopol polymers impart several desirable characteristics to toothpaste formulations like viscosity, yield value, low thixotropy and clarity.

Imparting viscosity at very low concentrations to thicken a system is a primary function of the polymers. Suspending abrasives and solid actives is accomplished through the build of yield value at low polymer concentrations. The combination of Carbopol

polymers' ability to build yield value with low thixotropy provides for a clean, non-stringing ribbon of toothpaste. From aesthetic and practical perspectives this means that Carbopol toothpaste formulations are pumpable, leave minimal solids residue on the tube rim, stand up well on the brush, and can be used in clear formulations.

Benefits in oral care applications

- Efficient co-binders at low usage levels.
- Suspending agents for non-soluble actives or excipients.
- Thicken peroxide gel systems while maintaining product stability.
- Compatible with commonly used formulation ingredients.

The large variety of applications as well as the steadily increasing number of research workers engaged in studies of Carbopol polymers due to their unique properties, have made significant contributions to many types of formulations and suggest that the potential of Carbopol as novel and versatile polymer will be even more significant in future.

7.2 POLYVINYL ALCOHOL

Structural formula

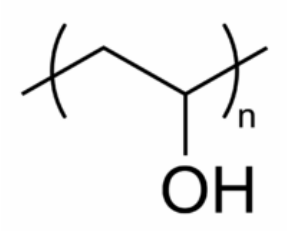


Fig : 6 Chemical structure of PVA.

7.2.1 Properties

Polyvinyl alcohol has excellent film forming, emulsifying, and adhesive properties. It is also resistant to oil, grease and solvent. It is odorless and nontoxic. It has high tensile strength and flexibility, as well as high oxygen and aroma barrier properties. However these properties are dependent on humidity, in other words, with higher humidity more water is absorbed. The water, which acts as a plasticizer, will then reduce its tensile strength, but increase its elongation and tear strength. PVA is fully degradable and is a quick dissolver. PVA has a melting point of 230°C and 180–190°C for the fully hydrolysed and partially hydrolysed grades. It decomposes rapidly above 200°C as it can undergo pyrolysis at high temperatures.

PVA is an ataxic material but exhibits crystallinity as the hydroxyl groups are small enough to fit into the lattice without disrupting it.

Molecular formula : $(C_2H_4O)_x$

Melting point : 230°C

Boiling point : 228°C

7.2.2 Uses

Some of the uses of polyvinyl alcohol include:

1. Adhesive and thickener material in latex paints, paper coatings, release liner, hairsprays, shampoos and glues.
2. Textile sizing agent
3. Feminine hygiene and adult incontinence products as a biodegradable plastic backing sheet.
4. As a mold release because materials such as epoxy do not stick to it.
5. As a water-soluble film useful for packaging.
6. Used in eye drops and hard contact lens solution as a lubricant.
7. Used in protective chemical-resistant gloves
8. Used as a fixative for specimen collection, especially stool samples
9. When doped with iodine, PVA can be used to polarize light.
10. As an embolization agent in medical procedures

7.3 P OLYVINYL PYRROLIDONE

Polyvinylpyrrolidone (**PNVP**, **PVP**, **povidone**, **polyvidone**) is a water-soluble polymer made from the monomer *N*-vinylpyrrolidone:

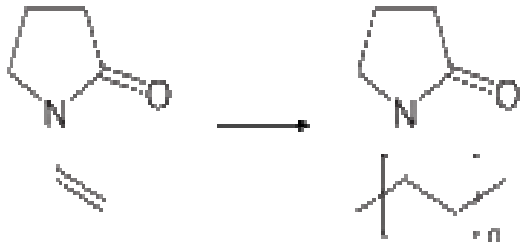


Fig : 7 Chemical structure of PVP

7.3.1 Properties

PVP is soluble in water and other polar solvents. In water it has the useful property of Newtonian viscosity. When dry it is a light flaky powder, which readily absorbs up to 40% of its weight in atmospheric water. In solution, it has excellent wetting properties and readily forms films. This makes it good as a coating or an additive to coatings.

7.3.2 Uses

The monomer is extremely toxic to aquatic life. However, the polymer PVP was used as a blood plasma expander for trauma victims after the first half of the 20th century.

It is used as a binder in many pharmaceutical tablets; it simply passes through the body when taken orally. PVP added to Iodine forms a complex (Povidone-iodine) that possesses disinfectant

properties. This complex is contained in various products like solutions, ointment, pessaries, liquid soaps and surgical scrubs.

PVP binds to polar molecules exceptionally well, owing to its polarity. This has led to its application in coatings for photo-quality ink-jet papers and transparencies, as well as in inks for inkjet printers.

PVP is also used in personal care products, such as shampoos and toothpastes, in paints, and adhesives that must be moistened, such as old-style postage stamps and envelopes. It has also been used in contact lens solutions and in steel-quenching solutions. PVP is the basis of the early formulas for hair sprays and hair gels, and still continues to be a component of some.

As a food additive, PVP is a stabilizer and has E number **E1201**. PVPP is **E1202**. It is also used in the wine industry as a fining agent for white wine.

In molecular biology, PVP can be used as a blocking agent during Southern blot analysis as a component of Denhardt's buffer. It is also exceptionally good at adsorbing polyphenols during DNA purification. Polyphenols are common in many plant tissues and can deactivate proteins if not removed and therefore inhibit many downstream reactions like PCR.

PVP is also used in many technical applications:

- as adhesive in glue stick and hot melts
- as special additive for batteries, ceramics, fiberglass, inks, inkjet paper and in the chemical-mechanical planarization process
- as emulsifier and disintegrant for solution polymerization
- as photo resist for cathode ray tubes (CRT)
- use in aqueous metal quenching
- for production of membranes, such as dialysis and water purification filters
- as binder and complexation agent in agro applications such as crop protection, seed treatment and coating
- as a thickening agent in tooth whitening gels,
- as an aid for increasing the solubility of drugs in liquid and semi-liquid dosage forms (syrups, soft gelatin capsules) and as an inhibitor of recrystallisation.

7.3.3 Cross-linked derivatives

A cross-linked form of PVP is also used as a disintegrant in pharmaceutical tablets. It is also known as cross-linked polyvinyl pyrrolidone, Polyvinyl Polypyrrolidone (**PVPP**), crospovidone, crospolividone. Basically, PVPP is a highly cross-linked version of PVP, which makes it insoluble in water but it still absorbs water and swells very rapidly and generate a swelling force. That is why it can be used a disintegrant in tablets. It is also used to bind impurities to remove them from solutions. It is also used as a fining to extract

impurities (via agglomeration followed by filtration). Using the same principle it is used to remove polyphenols in beer production and thus clear beers with stable foam are produced. PVPP can be used as well as a drug taken as a tablet or suspension and it absorbs compounds (so called Endotoxins) causing diarrhoea.

Molecular formula	:	$(C_6H_9NO)_n$
Molar mass	:	2.500 - 2.5000.000 $g \cdot mol^{-1}$
Appearance	:	white to light yellow, hygroscopic, amorphous powder
Density	:	1.2 g/ cm^3
Melting point	:	110 - 180 °C (glass temperature)

7.4 ETHYL CELLULOSE

Chemical name : Cellulose Ethyl Ether

Structural Formula :

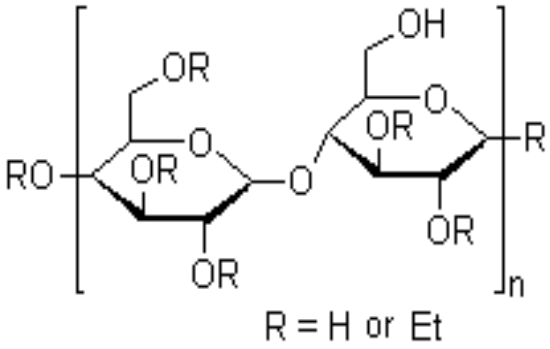


Fig : 8 Structure of Ethyl Cellulose

Functional Category:

Coating agent, flavoring fixative, tablet binders, tablet filler, viscosity increasing agent.

Description:

Ethyl cellulose is a tasteless, free flowing, white to light tan colored powder.

7.4.1 Typical Properties:

Density (bulk)

0.4g/cm^3

Solubility:

It is practically insoluble in glycerin, propylene glycol and water.

Specific Gravity:

1.12-1.15g/cm^3

Stability:

It is stable, slightly hygroscopic material, chemically resistant to alkalis. It is subject to oxidative degradation in presence of sunlight or UV light at elevated temperatures.

Incompatibility:

Incompatible with paraffin wax and microcrystalline wax.

7.4.2 Application:

- Ethyl Cellulose is widely used in oral and topical pharmaceutical formulation.
- It is used as a hydrophobic coating agent for tablets and granules.
- It is used to modify the release of a drug
- It is used to mask an unpleasant taste.
- It is used to improve stability of a formulation.

8. ANALYTICAL METHODS

8.1 PROCEDURE FOR STANDARD GRAPH OF NICORANDIL

Preparation of stock solution

100mg pure drug (Nicorandil-API) is dissolved in deionized water and made up to 100ml in a standard flask .From this, 10 ml of the drug solution is withdrawn and made up to 100ml with deionized water in a standard flask, to give the stock solution 100µg/ml.

From this solution, pipette out 1.0, 2.0, 3.0, 4.0 and 5.0 ml, which are transferred into a series of 10 ml volumetric flasks and the final volume was brought up to 10ml with deionized water to get concentrations of 10, 20, 30, 40, 50 µg /ml. A blank was also prepared. The absorbance was measured at 262nm and the standard graph was plotted concentration (µg/ml) Vs Absorbance. The results were given in Table 7 and Fig 8.

TABLE 7 : STANDARD GRAPH OF NICORANDIL

Concentration(µg/ml)	Absorbance at 262 nm
0	0.0000
10	0.1616
20	0.3339
30	0.5033
40	0.6621
50	0.8282

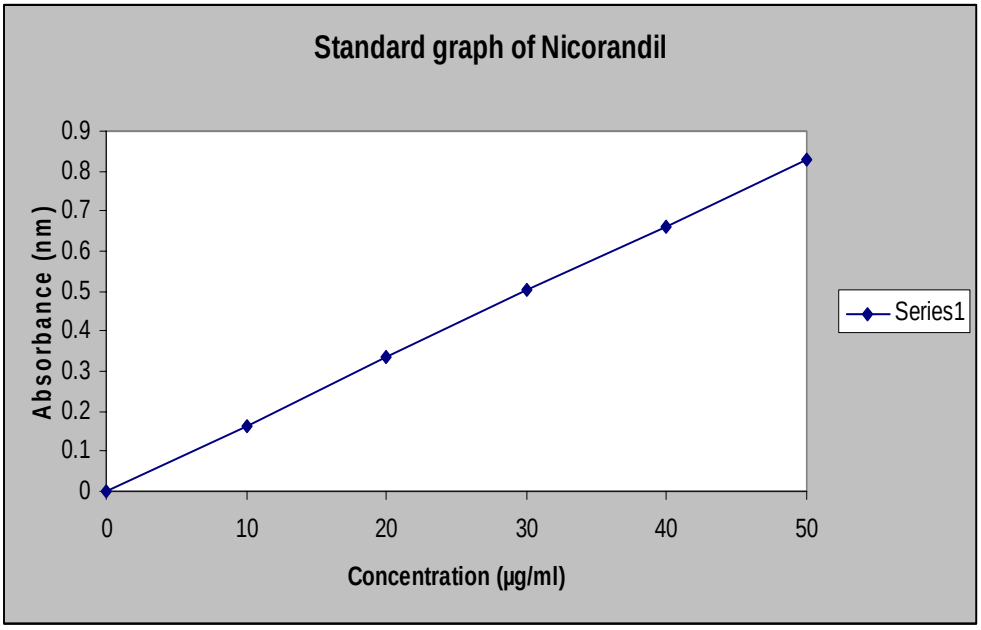


Fig :8 Standard Graph of Nicorandil

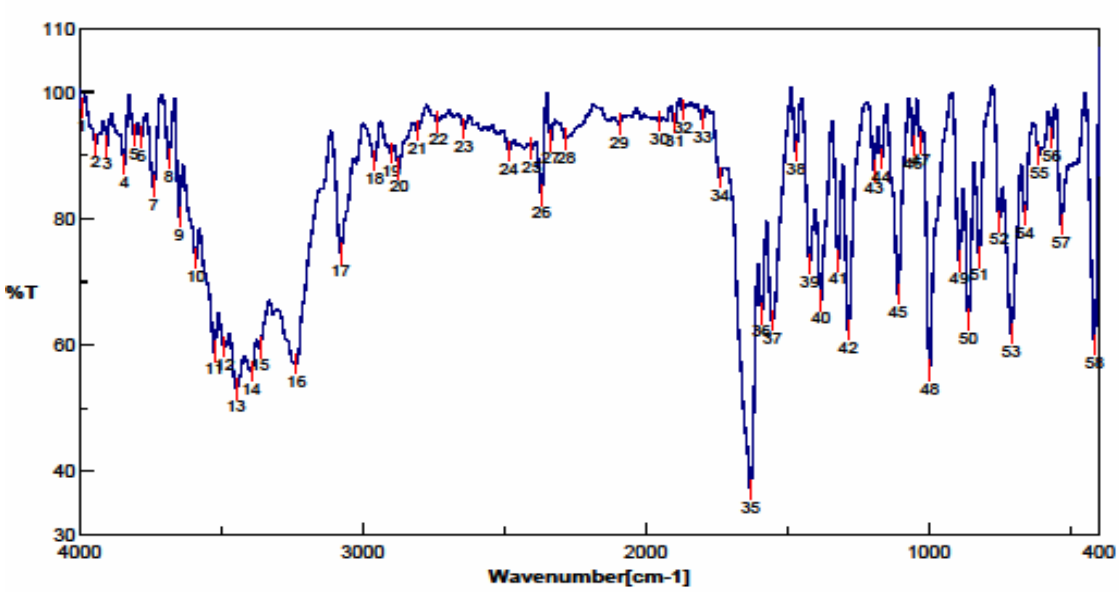
8.2 FT-IR COMPATIBILITY STUDIES

The drug (API) and the polymers used were subjected to FT-IR individually and in combination with polymers and checked for compatibility. The results were tested for incompatibility.

One of the requirements for the selection of suitable polymers or carriers for pharmaceutical formulation is its compatibility. Therefore in the present work a compatibility study was done by using Infra Red spectroscopy (IR) to find out if there is any possible chemical interaction between nicorandil and the polymers (carbopol-934, PVA, PVP and Ethyl cellulose).

IR spectral analysis

Weighed amount of the drug (3mg) was mixed thoroughly with 100mg of potassium bromide (dried at 40° -50° C) which was then compressed under 10 ton pressure in a hydraulic press to form a pellet which was then scanned from 4000 - 400^{-1}cm using FT-IR 410 PC spectrophotometer. The same procedure was repeated for polymers and formulations. The IR spectrum of nicorandil was compared with the IR spectrum of nicorandil and polymers. (Fig 10-15).



No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3992.89	97.4925	2	3943.71	91.7766	3	3903.22	91.4582
4	3842.47	88.5236	5	3806.79	93.1281	6	3781.72	92.8054
7	3739.3	85.1059	8	3686.26	89.5221	9	3648.66	80.2416
10	3589.84	73.712	11	3525.24	58.9677	12	3487.63	59.6701
13	3448.1	53.0691	14	3395.07	55.8791	15	3364.21	59.5966
16	3234.04	57.0265	17	3078.8	74.5085	18	2958.27	89.1721
19	2899.45	90.344	20	2872.45	87.8406	21	2806.88	93.9614
22	2734.57	95.3277	23	2642.96	94.1743	24	2483.87	90.6848
25	2403.83	91.0237	26	2370.09	83.7426	27	2336.34	92.3416
28	2283.3	92.5533	29	2095.28	94.9332	30	1952.57	95.4044
31	1899.54	95.0907	32	1869.65	97.2205	33	1801.19	95.6776
34	1739.48	86.4356	35	1631.48	37.1549	36	1591.95	64.9362
37	1555.31	63.8102	38	1471.42	90.6393	39	1422.24	72.7646
40	1383.68	67.0674	41	1321.96	73.2691	42	1286.29	62.3487
43	1195.65	87.5797	44	1168.65	89.4707	45	1110.8	67.9916
46	1056.8	91.5942	47	1029.8	91.9632	48	998.946	55.955
49	894.809	73.3347	50	862.025	63.9591	51	824.42	73.8943
52	753.066	79.5143	53	710.64	61.8076	54	662.428	80.5421
55	612.288	90.027	56	566.969	92.7683	57	534.185	78.9961
58	416.549	60.0832						

Fig :10 IR Spectrum of Nicorandil (API)

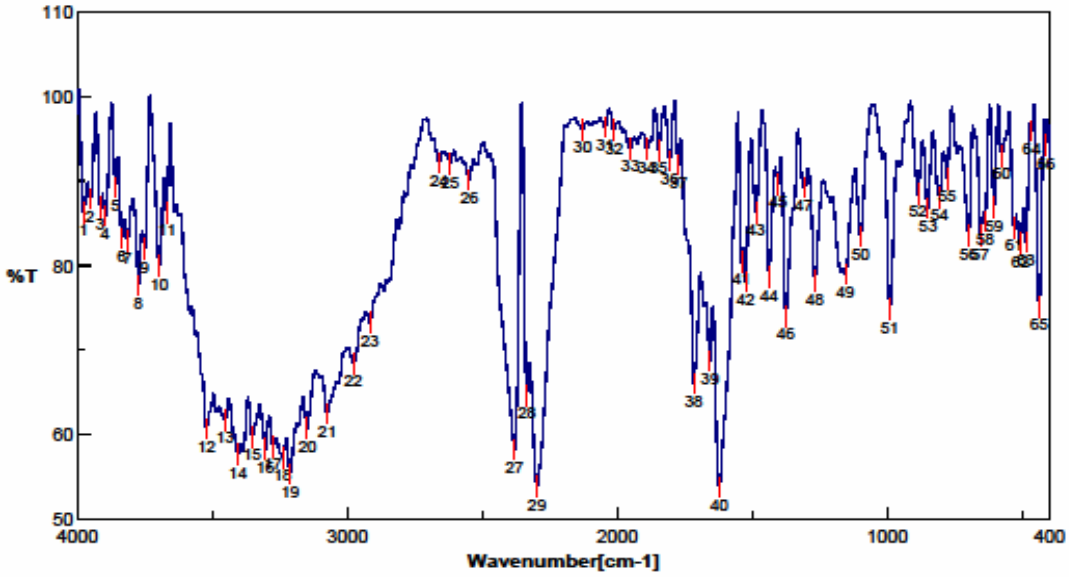


Fig :11 IR Spectrum of Nicorandil (API) and Carbopol 934

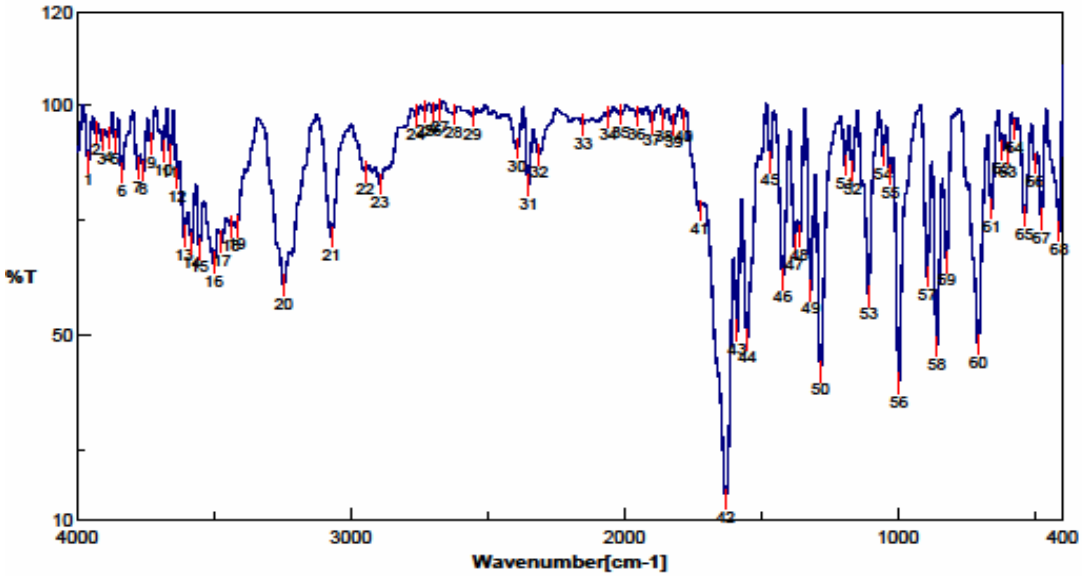


Fig :12 IR Spectrum of Nicorandil (API) and PVP

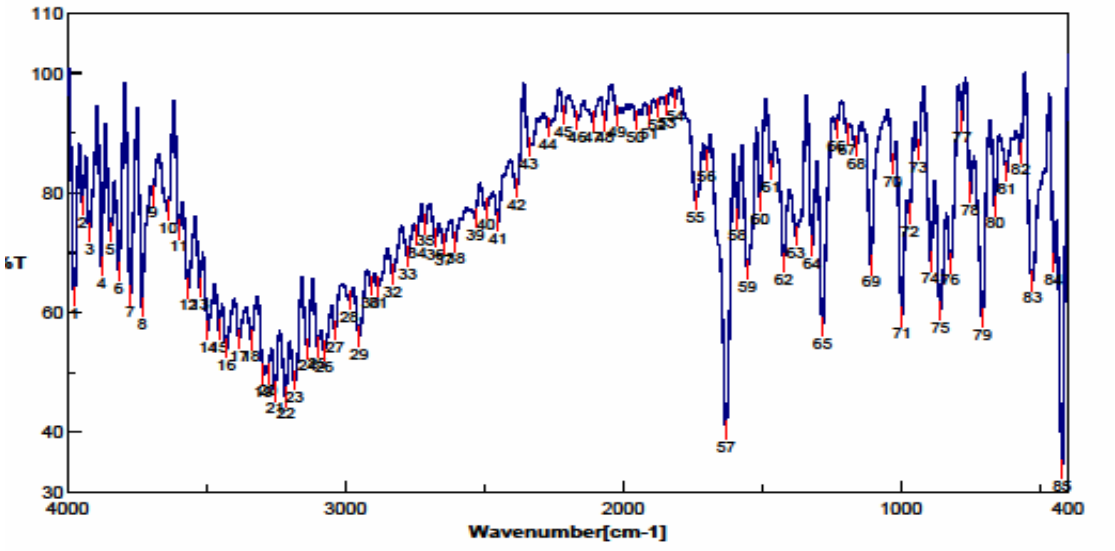


Fig :14 IR Spectrum of Nicorandil (API) and PVA

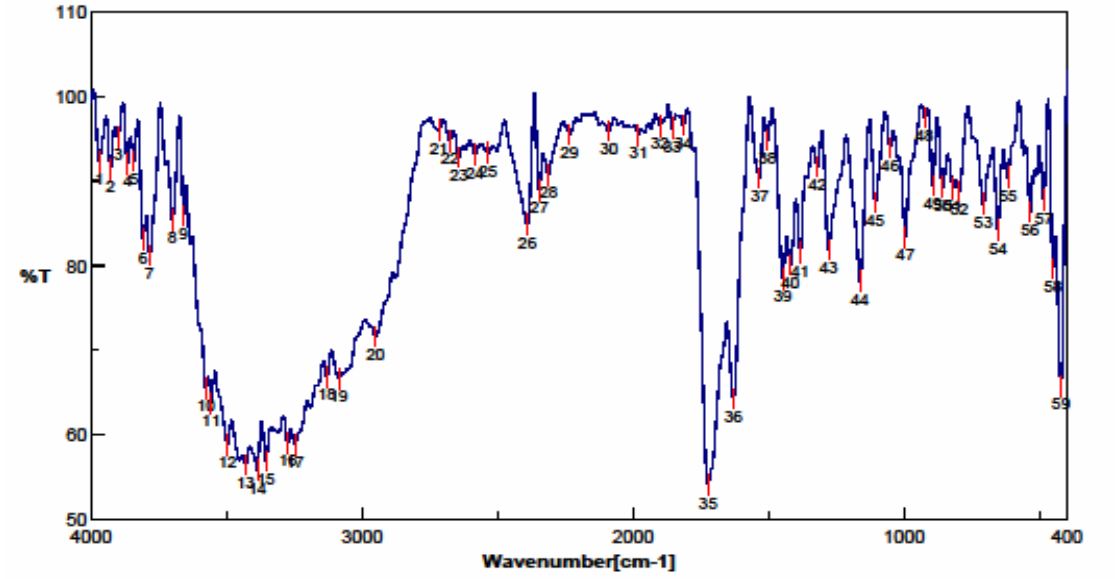


Fig :15 IR Spectrum of Nicorandil (API) and EC

9. EXPERIMENTAL METHODOLOGY

Hypertension and angina pectoris, the most common cardiovascular diseases, require constant monitoring. Potassium channel openers are presently considered an important class of drugs for hypertension and angina pectoris. The first therapeutic drug shown to possess ability to hyperpolarize smooth muscle cell membranes is nicorandil, a potent coronary vasodilator. Nicorandil is one of the emerging molecules in the case of hypertension and angina, successful treatment means maintenance of blood pressure at a normal physiological level, for which a constant and uniform supply of drug is desired. A novel drug delivery for the formulation of buccal tablet of Nicorandil by using polymers such as Carbopol 934 and PVP, which has good mucoadhesive properties, is developed by direct compression method.

Effect of backing layer on buccal tablet

Ethyl cellulose is used as backing layer, on one side of the buccal tablet to promote unidirectional release. In the absence of backing layer, some of the drug released escapes into the oral cavity; hence total mucosal drug release will be affected.

9.1 PROCEDURE FOR PREPARATION OF NICORANDIL BUCCAL TABLETS BY DIRECT COMPRESSION METHOD

Method I

Respective amount of the drug and polymers were blended together thoroughly in a mortar. Other excipients were added to this mixture and the final mixture subjected to direct compression in a single punch Tablet Punching machine. A suitable backing layer was coated on the back side of the tablet, to provide unidirectional release.

Table : 8 Composition and formulation code of various buccal tablets prepared by Method I

Formulation ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)
Nicorandil	3	3	3	5	3
Carbopol-934	120	120	100	120	120
PVP	80	80	80	80	0
PVA	0	0	50	0	0
Magnesium Stearate	q.s	q.s	q.s	q.s	q.s
Mannitol	q.s	q.s	q.s	q.s	q.s
β cyclodextrin	2	2	2	2	2
Ethyl Cellulose	Coated as Backing layer				

Method II

Bilayered tablets were prepared, core tablet compressed with a backing layer. Core tablet was prepared by compressing the drug with suitable ratios of polymers. Then, a backing layer of polymer is compressed onto the core tablet. The blended powder was then lightly compressed on 8mm flat faced punch using single punch tablet compression machine.

The upper punch was then removed and backing layer material was added over it and finally compressed at a constant compression force.

Table : 9 Composition and formulation code of various tablets prepared by Method II

Formulation ingredients	B_1 (mg)	B_2 (mg)	B_3 (mg)	B_4 (mg)
Nicorandil	3	5	3	3
Carbopol-934	120	120	80	20
PVP	80	80	20	180
PVA	0	0	0	0
Magnesium Stearate	q.s	q.s	q.s	q.s
Mannitol	q.s	q.s	q.s	q.s
β cyclodextrin	2	2	2	2
Backing Layer				
Ethyl cellulose	30	30	30	30

9.2 EVALUATION OF NICORANDIL-BUCCAL TABLETS

9.2.1 Weight variation test

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance, and the test was performed according to the official method as in BP. The weight variation allowed as per USP limit is 7.5%. The weights of individual tablets were within the BP limits. The results were shown in Table 10.

Table : 10 Weight variation of formulated Nicorandil buccal tablets

Formulation code	Wt Range of 20 tabs (mg)	Average weight (mg)	Limit range (±7.5%)
F1	247-260	253	245.5-260.5
F2	315-326	321	313.5-328.5
F3	243-257	250	242.5-257.5
F4	256-268	263	255.5-270.5
F5	229-242	236	228.5-243.5
B1	279-291	285	277.5-292.5
B2	282-293	288	280.5-295.5
B3	198-212	205	197.5-212.5
B4	269-283	276	268.5-283.5

9.2.2 Drug content assay

The prepared buccal tablets containing Nicorandil was tested for drug content uniformity as per specifications of IP 1996. Five tablets were weighed individually, and the drug was extracted in water. The drug content was determined as described. An accurately weighed amount of powdered nicorandil granules (100 mg) was extracted with water and the solution was filtered through 0.45-µ membrane (New Delhi, India). The absorbance was measured at 262 nm after suitable dilution. The results were shown in Table 11.

Table : 11 . Drug content uniformity of various nicorandil buccal tablets

Formulation	Absorbance (262nm)	Amount of Nicorandil content per buccal tablet	
		Amt (in mg)	Percentage Purity
F1	0.228	8.703	87.03
F2	0.256	9.713	97.71
F3	0.238	9.083	90.84
F4	0.241	9.198	91.98
F5	0.231	8.816	88.16
B1	0.244	9.313	93.13
B2	0.251	9.579	95.81
B3	0.254	9.694	96.94
B4	0.231	8.816	88.17

9.2.3. Thickness and diameter

Uniform compression force and volume of die fill leads to uniform thickness. From each batch, 3 buccal tablets were taken and checked with a electronic thick-ness gauge (Mitutoyo, New Delhi, India). Standard deviation was calculated and the results were given in Table 12 . .Similarly, three tablets were taken and checked for diameter using vernier, the results were given in Table 12.

9.2.4 Hardness

For each formulation, the hardness of 3 tablets were determined using the Monsanto hardness tester (Cad-mach, Ahmedabad, India), and the average was calculated and recorded in Table 12.

9.2.5 Friability

For each formulation, the friability of 10 tablets were determined using the Roche friabilator (Camp-bell Electronics, Mumbai, India), respectively (Table 12).

$$\% \text{ Friability} = \frac{\text{Loss of weight}}{\text{Initial weight}} \times 100$$

Table :12 . Thickness, hardness and % friability of various formulated nicorandil buccal tablets

Sl. No.	Formulation code	Thickness (mm)	Hardness (kg/cm2)	Friability (%)
1	F1	2.42 ± 0.2	7.5 ± 0.14	0.75
2	F2	2.93 ± 0.1	6.5 ± 0.09	0.69
3	F3	2.14 ± 0.3	8.5 ± 0.11	0.40
4	F4	2.25 ± 0.1	7.5 ± 0.13	0.48
5	F5	1.83 ± 0.3	6.5 ± 0.18	0.13
6	B1	2.22 ± 0.2	8.0 ± 0.12	0.17
7	B2	2.27 ± 0.2	7.0 ± 0.23	0.28
8	B3	2.01 ± 0.1	8.5 ± 0.14	1.63
9	B4	2.73 ± 0.2	9.0 ± 0.11	0.76

n=3; ± Sd

9.3 FT-IR compatibility studies

The drug (API) and the polymers used were subjected to FT-IR individually and in combination with polymers and checked for compatibility. The results were tested for incompatibility.

One of the requirements for the selection of suitable polymers or carriers for pharmaceutical formulation is its compatibility. Therefore in the present work a compatibility study was done by using Infra Red spectroscopy (IR) to find out if there is any possible chemical interaction between nicorandil and the polymers (carbopol-934,PVA,PVP and Ethyl cellulose).

IR spectral analysis

Weighed amount of the drug (3mg) was mixed thoroughly with 100mg of potassium bromide (dried at 40° -50° C) which was then compressed under 10 ton pressure in a hydraulic press to form a pellet which was then scanned from 4000 - 400^{-1}cm using FT-IR 410 PC spectrophotometer. The same procedure was repeated for polymers and formulations. The IR spectrum of nicorandil was compared with the IR spectrum of formulation. The IR spectrum of the formulations F1-F5 and B1-B4 are given in Fig 16-24.

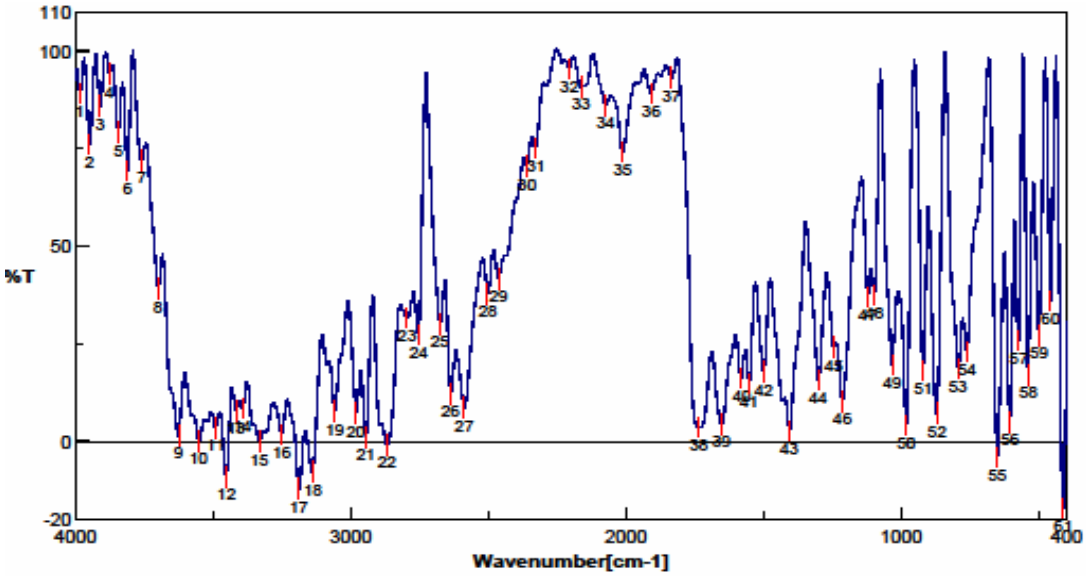


Fig :16 IR SPECTRUM OF F1

***F1- Composition: Nicorandil 3mg, CP 120mg, PVP 80mg, EC qs**

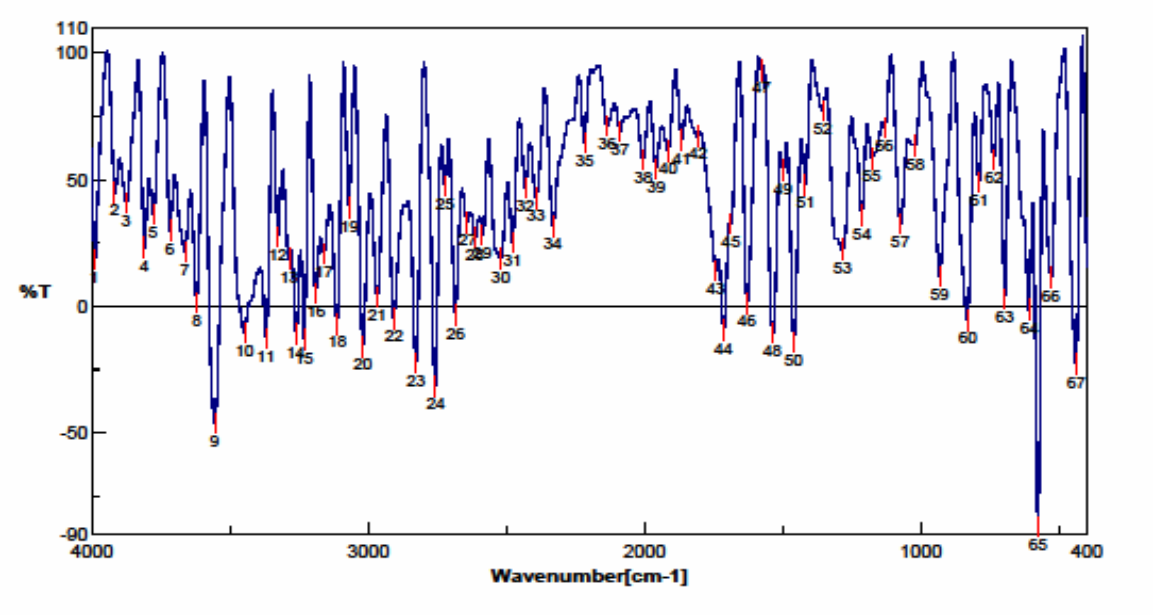


Fig : 17 IR SPECTRUM OF F2

***F2- Composition:Nicorandil 3mg, CP 100mg, PVP 80mg, EC q.s**

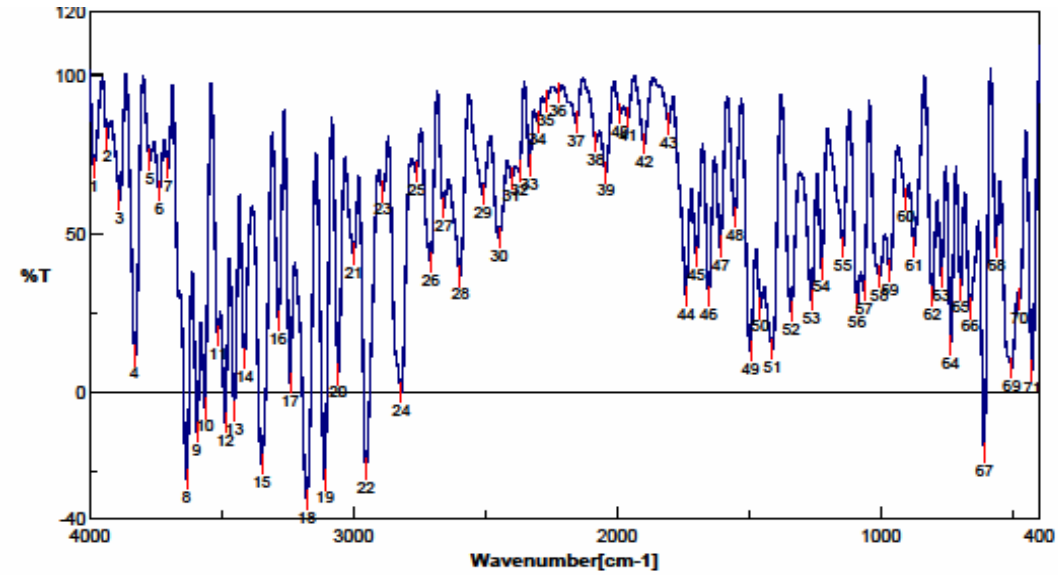


Fig :18 IR SPECTRUM OF F3

***F3- Composition: Nicorandil 3mg, CP 120mg, PVP 80mg, PVA 50mg, EC q.s**

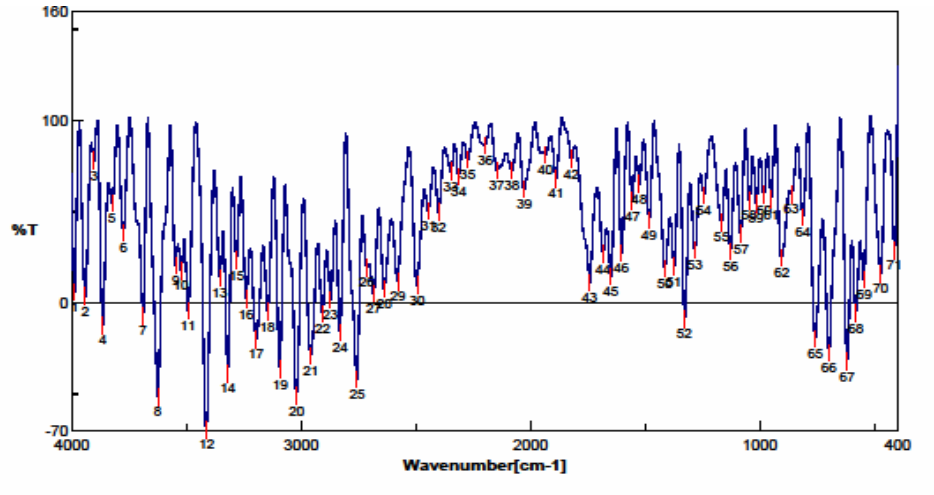


Fig :19 IR SPECTRUM OF F4

***F4- Composition: Nicorandil 5mg, CP 120mg, PVP 80mg, EC q.s**

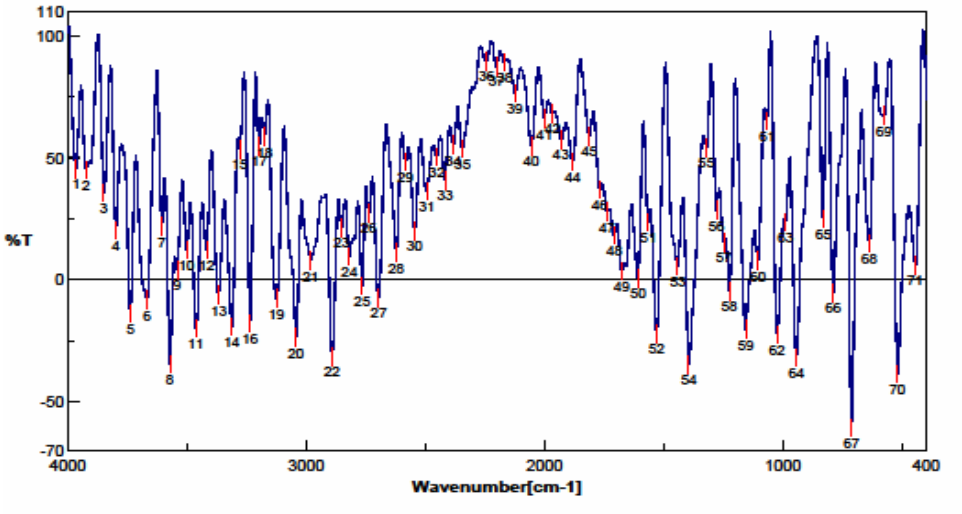


Fig : 20 IR SPECTRUM OF F5

***F5- Composition: Nicorandil 3mg, CP 120mg, EC q.s.**

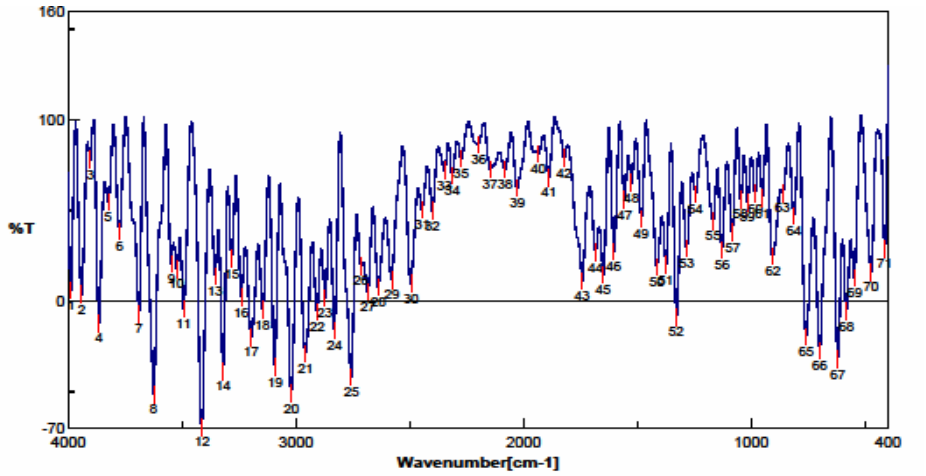


Fig : 21 IR SPECTRUM OF B1

*** B1- Composition: Nicorandil 3mg, CP 120mg, PVP 80mg, EC 30mg**

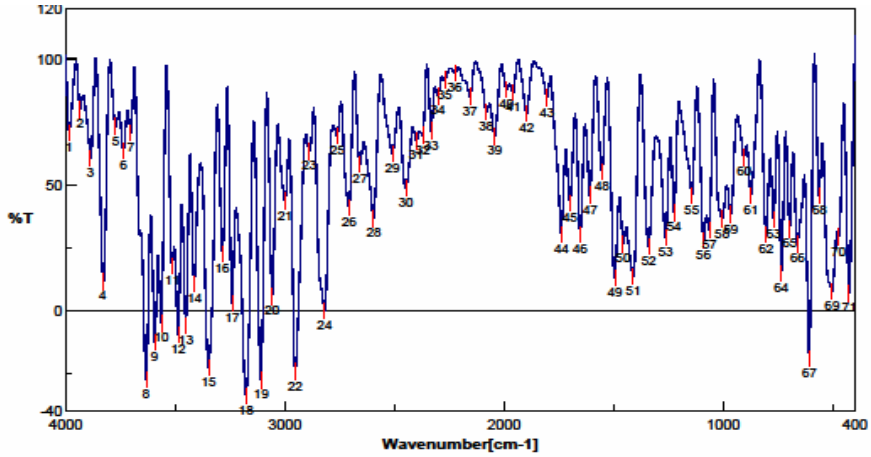


Fig :22 IR SPECTRUM OF B2

*** B2- Composition: Nicorandil 3mg, CP 120mg, PVP 80mg, EC q.s**

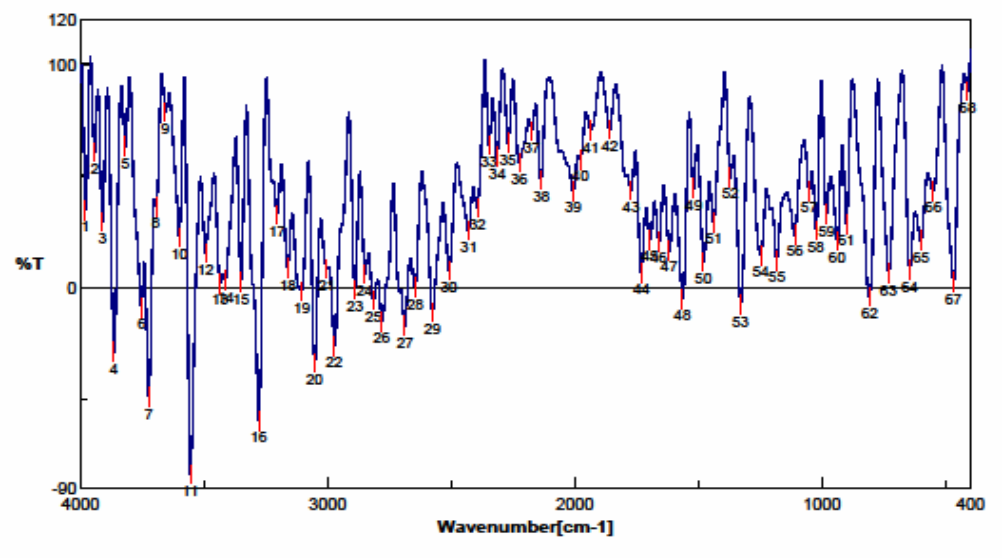


Fig : 23 IR SPECTRUM OF B3

***B3 - Composition: Nicorandil 3mg, CP 80mg, PVP 20mg, EC q.s**

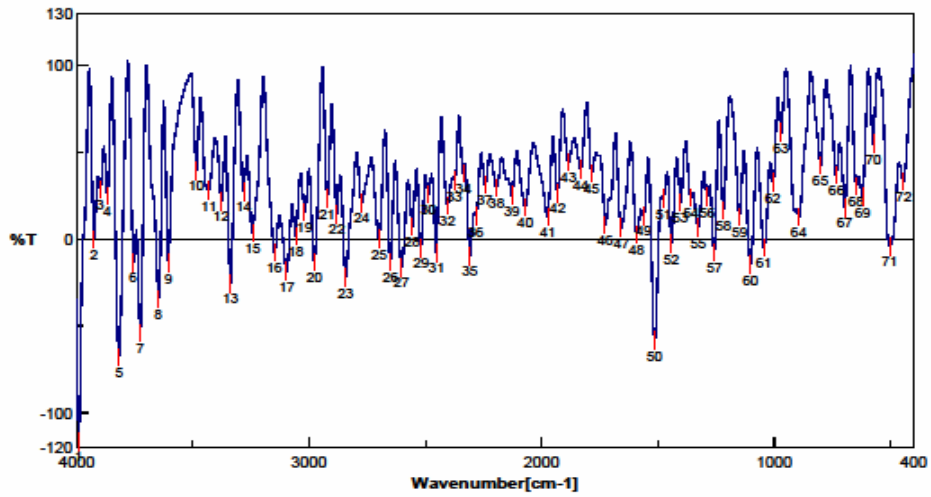


Fig : 24 IR SPECTRUM OF B4

***B4- Composition: Nicorandil 3mg, CP 20mg, PVP 180mg, EC q.s**

9.4 *IN-VITRO* DRUG RELEASE STUDIES

The *in-vitro* dissolution studies were carried out using USP apparatus type II (Tab-Machines, Mumbai, India) at 75 rpm. The dissolution medium consisted for the phosphate buffer pH 6.8 (250 ml), maintained at 37°C ± 0.5°C. The formulated tablets containing Nicorandil equivalent to 3mg and 5mg were taken and kept in the dissolution medium and the paddle type stirrer was adjusted to 75 rpm. 5ml aliquot dissolution media was withdrawn at intervals and volume withdrawn was replaced with fresh quantity of dissolution media. The drug release at different time intervals (1h, 2h, 3h, 4h, 5h, 6h, 7h, and 8h) was measured by diode array UV-visible spectrophotometer at 262 nm.

The percentage of Nicorandil dissolved at various time intervals was calculated and plotted against time. The results are shown in Tables 13-21 and Fig 25-33.

Table : 13 Dissolution profile of the buccal formulation F1* at pH 6.8 at different time intervals

F1 Time (hr)	Absorbance (262nm)	C (µ/ml)	C (mg/250ml)	Cumulative %release
1	0.05	3.5	0.875	29.17± 0.39
2	0.055	4.2	1.05	35.00 ± 0.74
3	0.0682	4.8	1.2	40.00 ± 0.46
4	0.0754	5.3	1.325	44.17 ± 0.62
5	0.0781	5.5	1.375	45.83 ± 0.86
6	0.0824	5.8	1.45	48.33 ± 1.2
7	0.0931	6.1	1.525	50.83 ± 0.78
8	0.1276	8.8	2.2	73.33 ± 1.34

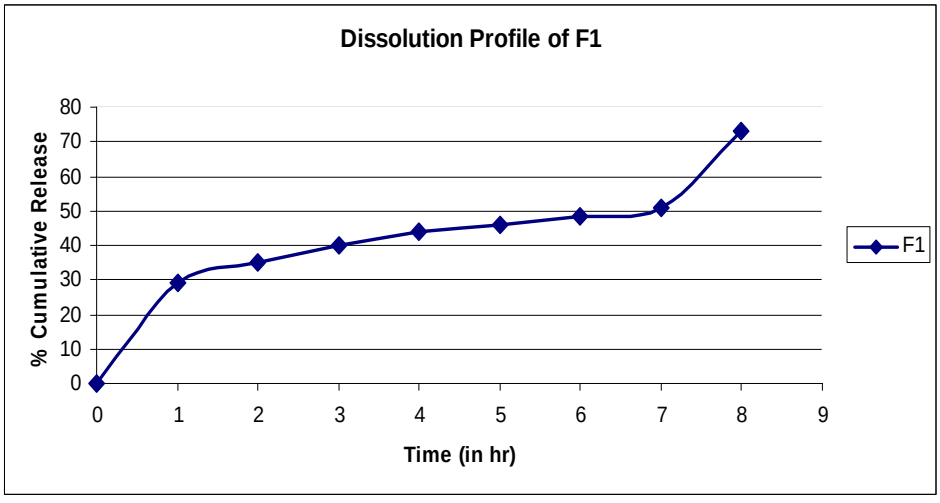


Fig : 25. Graph showing dissolution profile of F1

***F1- Composition: Nicorandil 3mg, CP 120mg, PVP 80mg, EC qs**

Table :14 Dissolution profile of the buccal formulation F2* at pH 6.8 at different time intervals

F2 Time (hr)	Absorbance (262nm)	C (µ/ml)	C (mg/250ml)	Cumulative %release
1	0.0158	2.2	0.55	18.33 ± 0.12
2	0.0475	3.6	0.9	30.00 ± 0.54
3	0.0695	4.35	1.0875	36.25 ±0.09
4	0.0721	4.52	1.13	37.67 ±0.86
5	0.0843	5.34	1.335	44.50 ±1.08
6	0.0927	5.65	1.4125	47.08 ±0.56
7	0.1098	6.34	1.585	52.83 ±0.78
8	0.1134	8.2	2.05	68.33 ±1.21

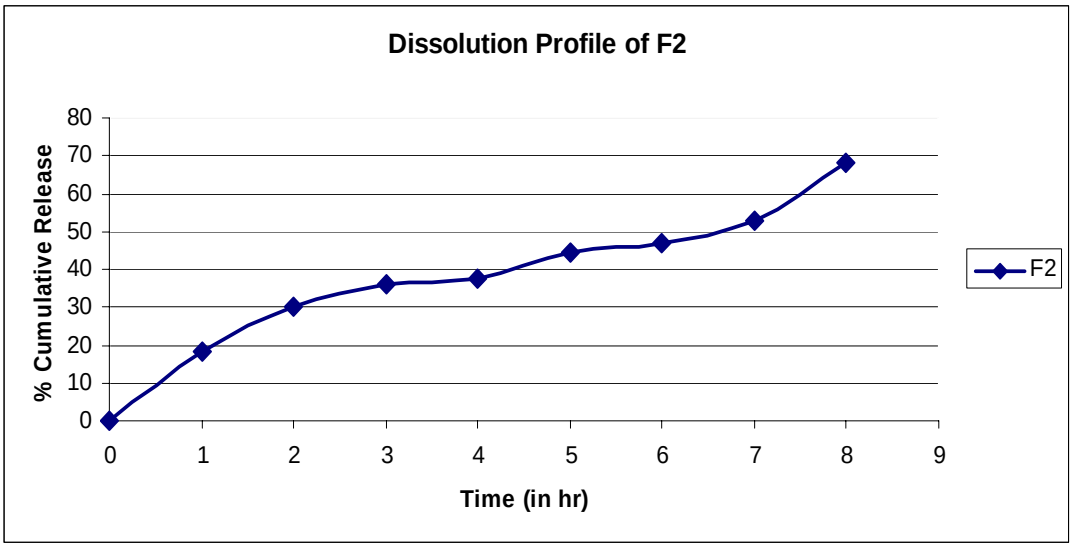


Fig : 26. Graph showing dissolution profile of F2

***F2- Composition: Nicorandil 3mg, CP 100mg, PVP 80mg, EC q.s**

Table : 15 .Dissolution profile of the buccal formulation F3* at pH 6.8 at different time intervals

F3 Time (hr)	Absorbance (262nm)	C (µ/ml)	C (mg/250ml)	Cumulative %release
1	0.0667	4.2	1.05	35.00 ± 0.45
2	0.116	7.5	1.875	62.50 ± 0.51
3	0.128	8.4	2.1	70.00 ± 1.52
4	0.1325	8.6	2.15	71.67 ± 1.09
5	0.1384	8.8	2.2	73.33 ± 0.86
6	0.1412	9.1	2.275	75.83 ± 0.77
7	0.1467	9.4	2.35	78.33 ± 0.64
8	0.1481	9.7	2.425	80.83 ± 0.93

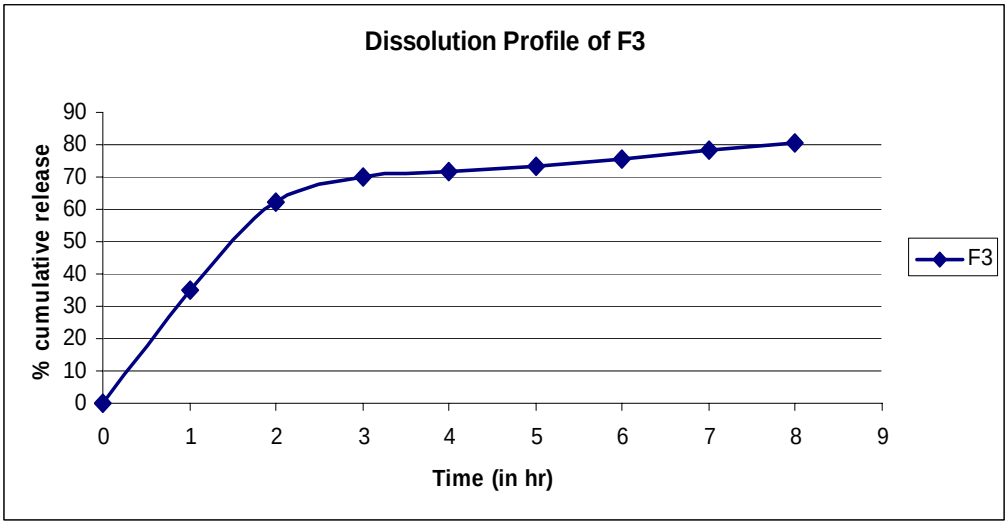


Fig : 27. Graph showing dissolution profile of F3

***F3- Composition: Nicorandil 3mg, CP 120mg, PVP 80mg, PVA 50mg, EC q.s**

Table :16. Dissolution profile of the buccal formulation F4* at pH 6.8 at different time intervals

F4 Time (hr)	Absorbance (262nm)	C (µ/ml)	C (mg/250ml)	Cumulative %release
1	0.1097	5.8	1.45	29.00 ± 0.33
2	0.1102	6.2	1.55	31.00 ± 0.65
3	0.1256	7.8	1.95	39.00 ± 0.58
4	0.1433	9.8	2.45	49.00 ± 0.42
5	0.1642	11.1	2.78	55.50 ± 0.96
6	0.2068	12.9	3.23	64.50 ± 1.21
7	0.2136	14.3	3.58	71.50 ± 1.10
8	0.2534	15.8	3.95	79.00 ± 0.52

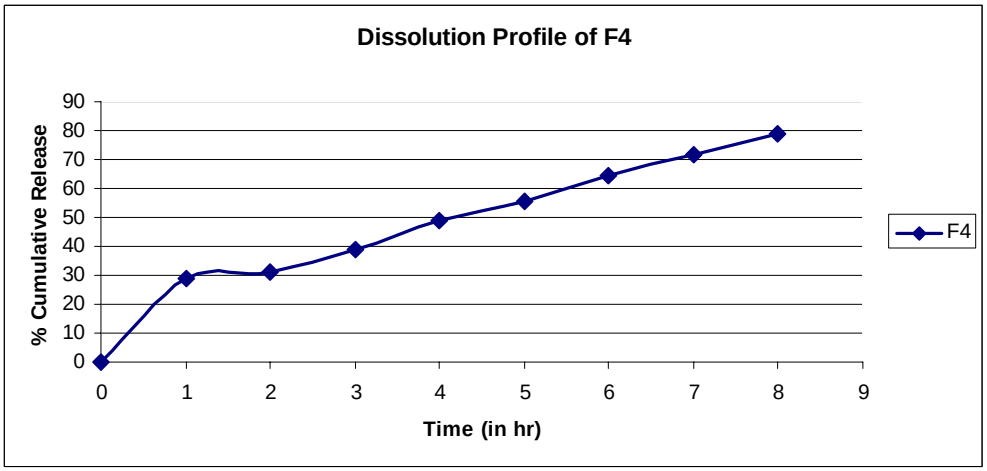


Fig : 28. Graph showing dissolution profile of F4

***F4: Composition: Nicorandil 5mg, CP 120mg, PVP 80mg, EC q.s**

Table : 17 Dissolution profile of the buccal formulation F5* at pH 6.8 at different time intervals

F5 Time (hr)	Absorbance (262nm)	C (µ/ml)	C (mg/250ml)	Cumulative %release
1	0.0361	2.2	0.55	18.33 ± 0.48
2	0.0529	2.5	0.625	20.83 ± 0.89
3	0.0762	3.8	0.95	31.66 ± 0.73
4	0.0893	3.9	0.975	32.50 ± 1.3
5	0.0912	4.1	1.025	34.17 ± 0.65
6	0.0936	4.7	1.175	39.17 ± 0.33
7	0.1243	7.5	1.875	62.50 ± 0.55
8	0.1336	8.9	2.225	68.17 ± 0.68

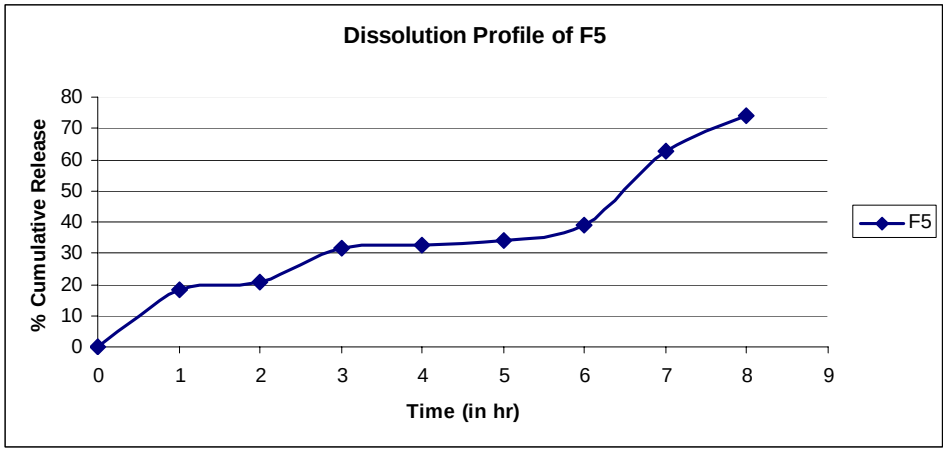


Fig :29. Graph showing dissolution profile of F5

***F5- Composition: Nicorandil 3mg, CP 120mg, EC q.s.**

Table : 18. Dissolution profile of the buccal formulation B1* at pH 6.8 at different time intervals

B1 Time (hr)	Absorbance (262nm)	C (µ/ml)	C (mg/250ml)	Cumulative %release
1	0.0391	2.2	0.55	18.33 ± 0.44
2	0.0723	3.6	0.9	30.00 ± 0.72
3	0.0942	4.8	1.2	40.00 ± 0.12
4	0.1288	6.8	1.7	56.67 ± 0.34
5	0.1312	7.1	1.775	59.17 ± 0.32
6	0.1342	7.8	1.95	65.00 ± 0.88
7	0.1377	8.6	2.15	71.67 ± 0.81
8	0.1413	9.1	2.275	75.83 ± 1.20

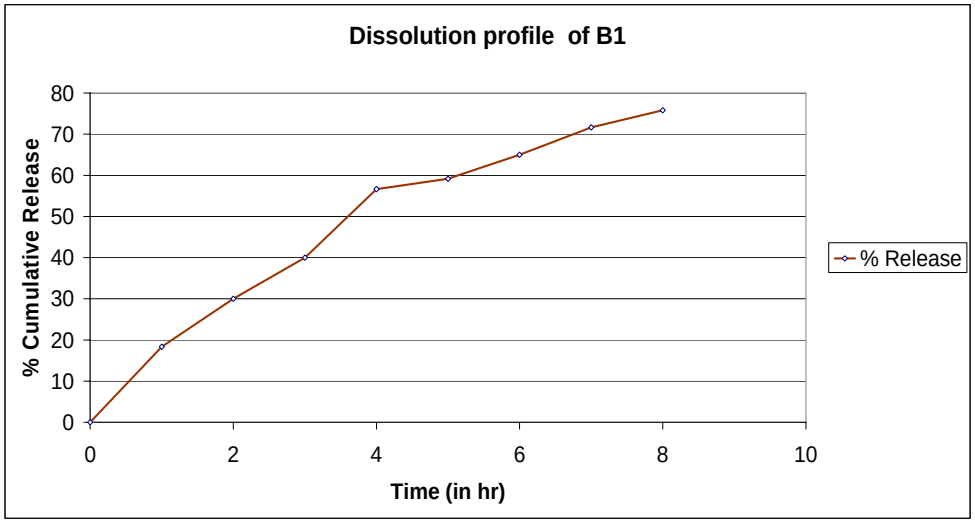


Fig : 30 Graph showing dissolution profile of B1

*** B1- Composition: Nicorandil 3mg, CP 120mg, PVP 80mg, EC 30mg**

Table :19 Dissolution profile of the buccal formulation B2* at pH 6.8 at different time intervals

Time (hr)	Absorbance (262nm)	C (µ/ml)	C (mg/250ml)	Cumulative %release
1	0.0984	6.7	1.675	33.50 ± 0.73
2	0.1527	9.8	2.45	49.00 ± 0.88
3	0.2074	12.8	3.2	64.00 ± 0.34
4	0.2169	14.7	3.675	73.50 ± 0.23
5	0.2272	15.2	3.8	76.00 ± 0.56
6	0.2342	16.1	4.025	80.50 ± 0.78
7	0.2481	16.7	4.175	83.50 ± 1.07
8	0.2711	17.4	4.35	87.00 ± 1.03

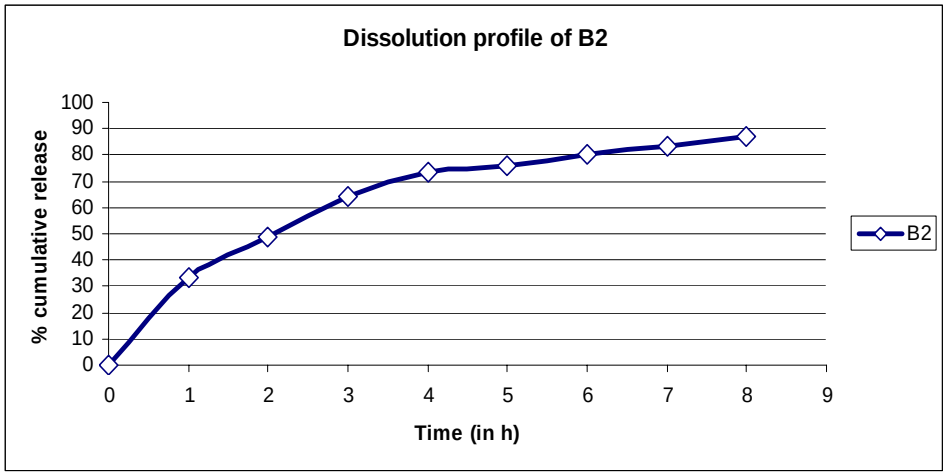


Fig : 31 Graph showing dissolution profile of B2

*** B2- Composition: Nicorandil 3mg, CP 120mg, PVP 80mg, EC q.s**

Table :20 Dissolution profile of the buccal formulation B3* at pH 6.8 at different time intervals

Time (hr)	Absorbance (262nm)	C (µ/ml)	C (mg/250ml)	Cumulative %release
1	0.0323	2.1	0.525	17.50 ± 0.68
2	0.1288	7.6	1.9	63.33 ± 0.87
3	0.1432	7.7	1.925	64.17 ± 0.32
4	0.1664	8.1	2.025	67.50 ± 0.64
5	0.1695	8.2	2.05	68.33 ± 0.95
6	0.1723	9.6	2.4	80.00 ± 1.22
7	0.1746	9.7	2.425	80.83 ± 0.43
8	0.1792	9.8	2.45	81.67 ± 0.69

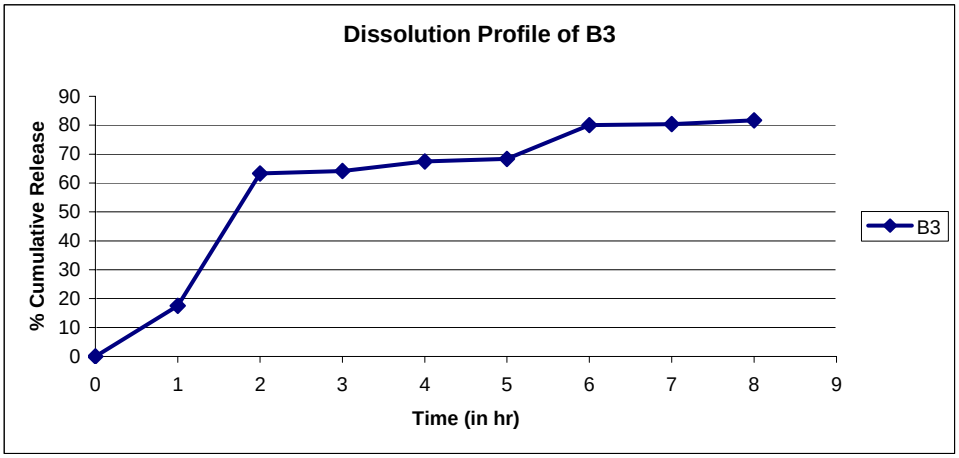


Fig : 32. Graph showing dissolution profile of B3

***B3 - Composition: Nicorandil 3mg, CP 80mg, PVP 20mg, EC q.s**

Table : 21. Dissolution profile of the buccal formulation B4* at pH 6.8 at different time intervals

Time (hr)	Absorbance (262nm)	C (µ/ml)	C (mg/250ml)	Cumulative %release
1	0.8765	5.8	1.45	48.33 ± 0.70
2	0.9504	6.3	1.575	52.50 ± 0.62
3	0.1092	7.2	1.8	60.00 ± 0.85
4	0.1148	7.6	1.9	63.33 ± 1.40
5	0.1151	8.1	2.025	67.50 ± 0.87
6	0.1285	8.5	2.125	70.83 ± 0.61
7	0.1342	8.8	2.2	73.33 ± 0.45
8	0.1547	9.2	2.3	76.67 ± 0.72

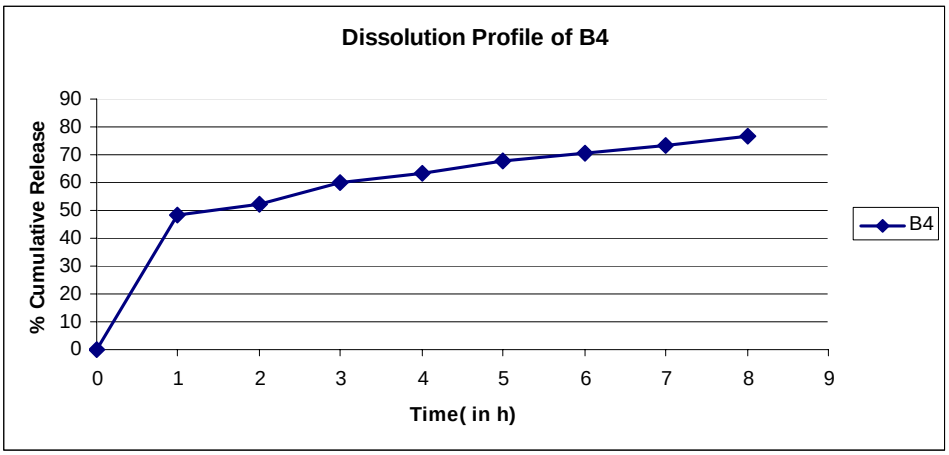


Fig : 33 Graph showing dissolution profile of B4

***B4- Composition: Nicorandil 3mg, CP 20mg, PVP 180mg, EC q.s**

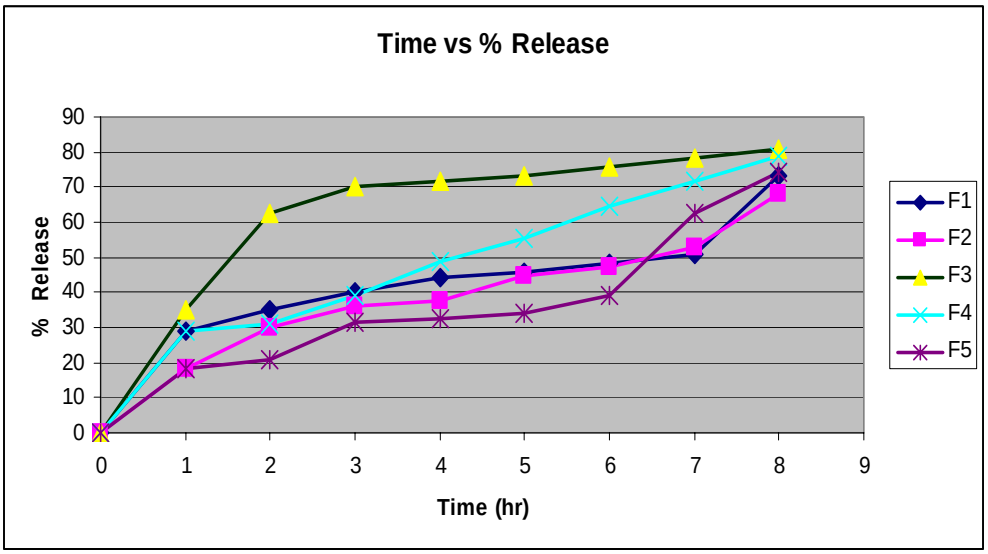


Fig : 34 Comparative graph showing the invitro release of nicorandil buccal tablets of F1, F2, F3, F4 and F5

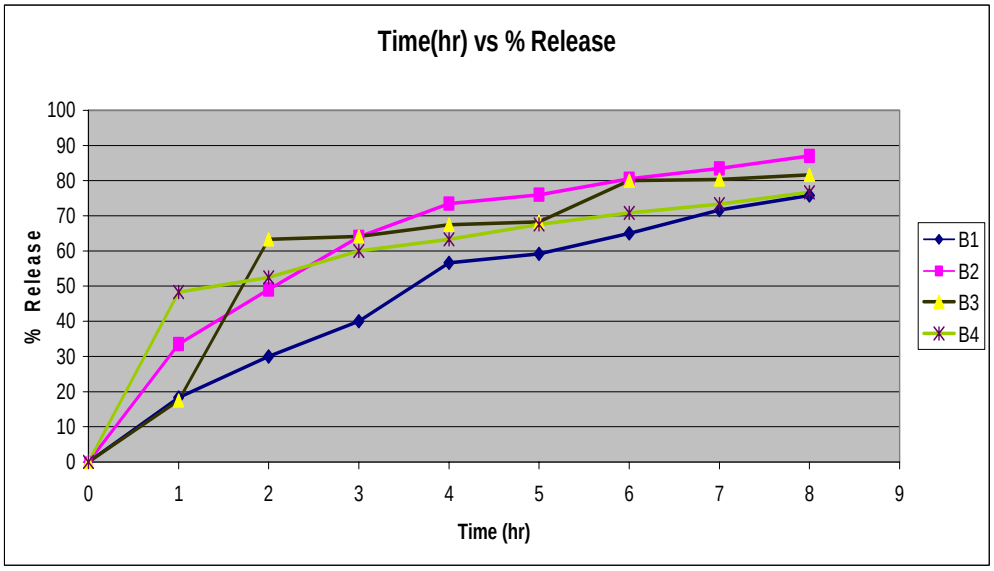


Fig : 35 Comparative graph showing the invitro release of nicorandil buccal tablets of B1,B2,B3 and B4

9.5 DISSOLUTION KINETICS OF DRUG RELEASE

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in various kinetic models: Zero order (Equation 1) as cumulative amount of drug released vs time, First order (Equation 2) as log cumulative percentage of drug remaining vs time, Higuchi's model (Equation 3) as cumulative percentage of drug released vs square root of time and Korsmeyer's (Equation 4) log cumulative percentage of drug released vs. log time

$$C = K^{o} t. \qquad \text{(Equation 1)}$$

Where K^{o} is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K0 and intercept the origin of the axes.

$$LogC = LogCo - kt/2{:}303 \qquad \text{(Equation 2)}$$

Where C0 is the initial concentration of drug, k is the first order constant, and t is the time.

$$Q = Kt\ ½ \qquad \text{(Equation 3)}$$

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Drug release were plotted in Korsmeyer et al's equation (Equation 4) as log cumulative percentage of drug released vs log

time, and the exponent n was calculated through the slope of the straight line.

$$Mt/M\infty = Ktn \qquad \text{(Equation 4)}$$

Where $Mt/M\infty$ is the fractional solute release, t is the release time, K is a kinetic constant.

Table: 22 Drug release kinetics for Nicorandil buccal Tablets

Formulation code	Zero Order R^2	First Order R^2	Higuchi's Plot R^2	Korsmeyer's Plot R^2
F1	0.984	0.973	0.996	0.991
F2	0.983	0.943	0.988	0.977
F3	0.966	0.992	0.993	0.942
F4	0.953	0.952	0.959	0.871
F5	0.966	0.990	0.990	0.925
B1	0.969	0.977	0.986	0.937
B2	0.834	0.843	0.994	0.956
B3	0.976	0.976	0.967	0.974
B4	0.972	0.956	0.984	0.949

In vitro data obtained for buccal tablets containing nicorandil were used to determine the dissolution kinetics. The drug release data of nicorandil were fitted to models representing Zero order (cumulative amount of drug released vs time), First order (log cumulative percentage of drug remaining vs time), Higuchi's (cumulative percentage of drug released vs square root of time), and

Korsmeyer's equation (log cumulative percentage of drug released vs log time) kinetics to know the release mechanisms. The data were processed for regression analysis using MS-EXCEL statistical functions. These data indicated that the drug release followed the diffusion controlled model as described by Higuchi's square root of time equation.

The chart of the formulation having best release characteristics in each method was plotted (Fig. 36-43). The formulation showing good release kinetics was found to be **F4** (Method I) and **B2** (Method II).

F4

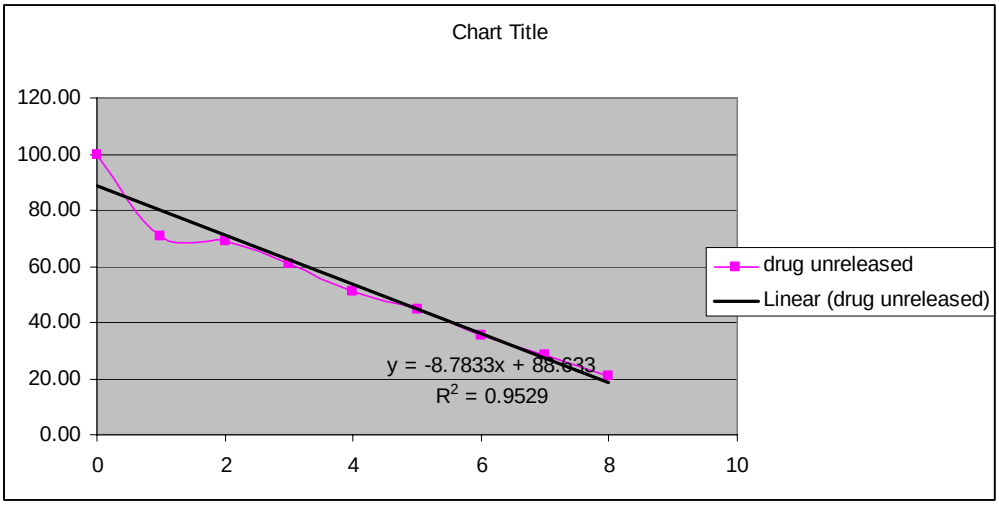


Fig :36 Graph showing first order kinetics of F4 buccal tablets.
***F4- Composition: Nicorandil 5mg, CP 120mg, PVP 80mg, EC q.s**

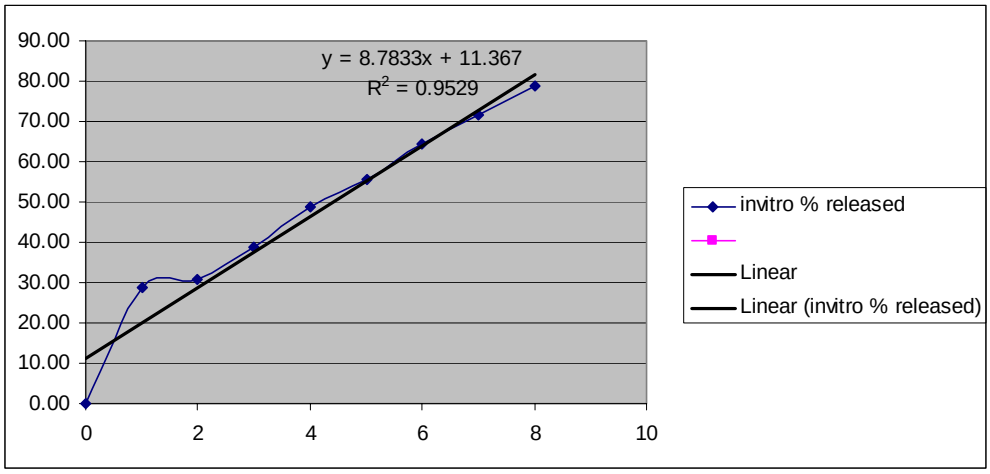


Fig : 37 . Graph showing zero order kinetics of F4 buccal tablets.

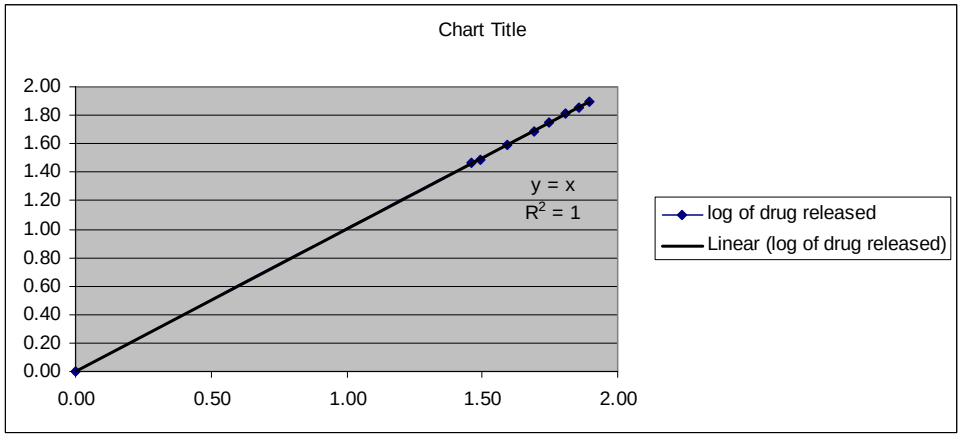


Fig : 38 Graph showing kosermeyer order kinetics of F4 buccal tablets

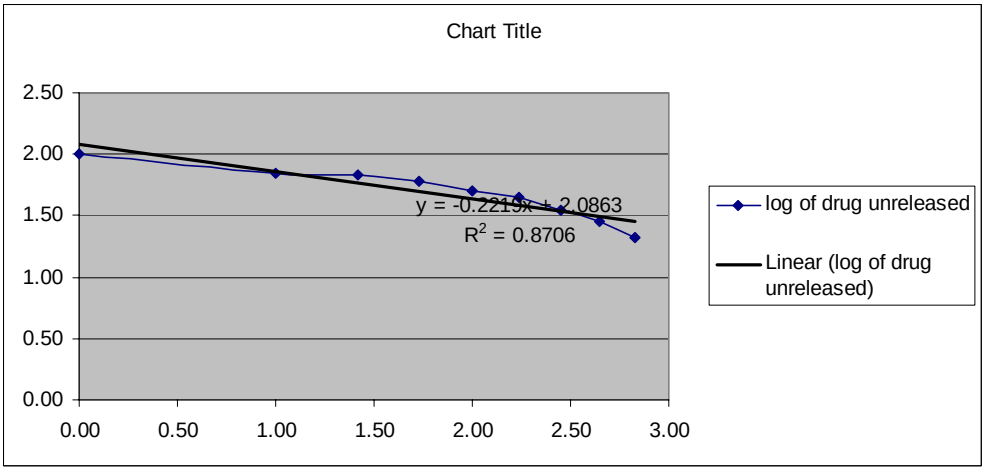


Fig : 39 Graph showing Higucchi's kinetics of F4 buccal tablets

B2

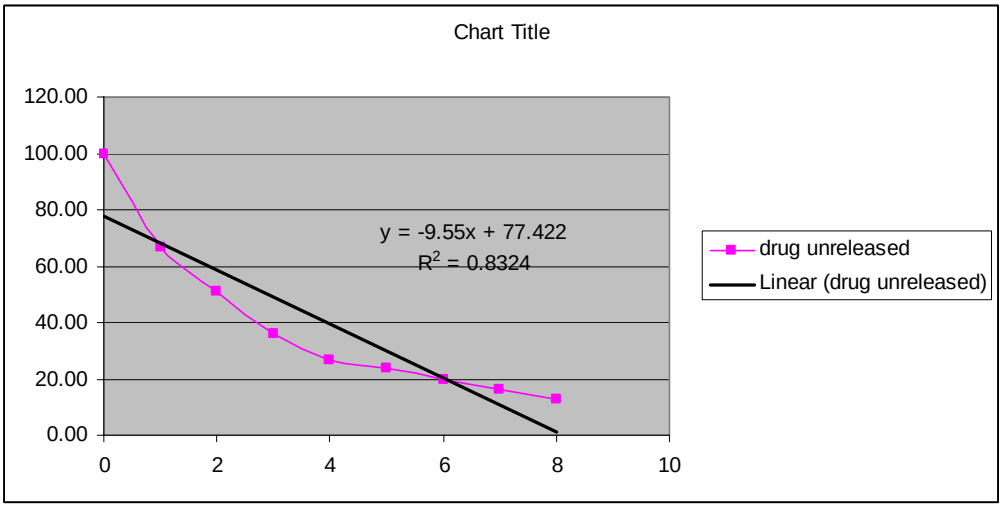


Fig : 40 Graph showing first order kinetics of B2 buccal tablets (* B2- Composition: Nicorandil 3mg, CP 120mg, PVP 80mg, EC q.s)

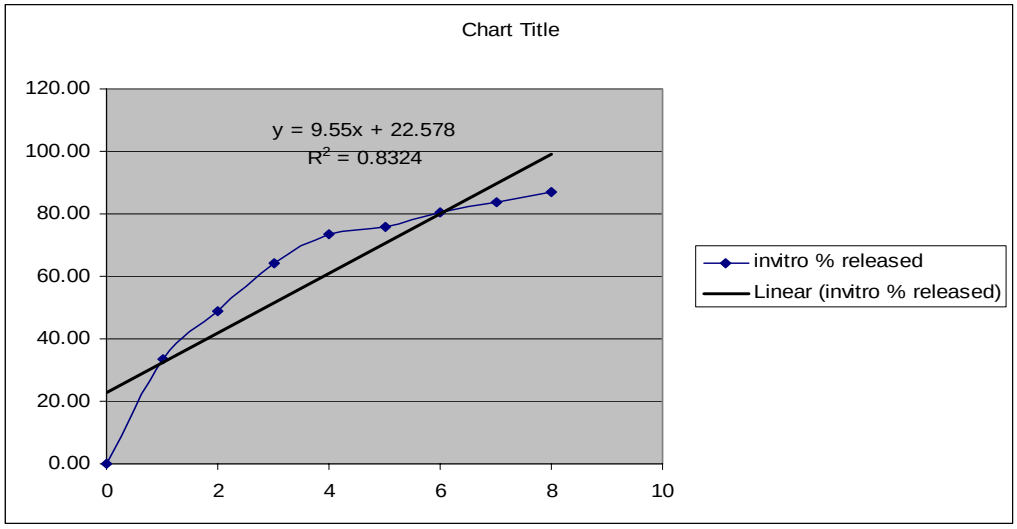


Fig : 41 Graph showing zero order kinetics of B2 buccal tablets

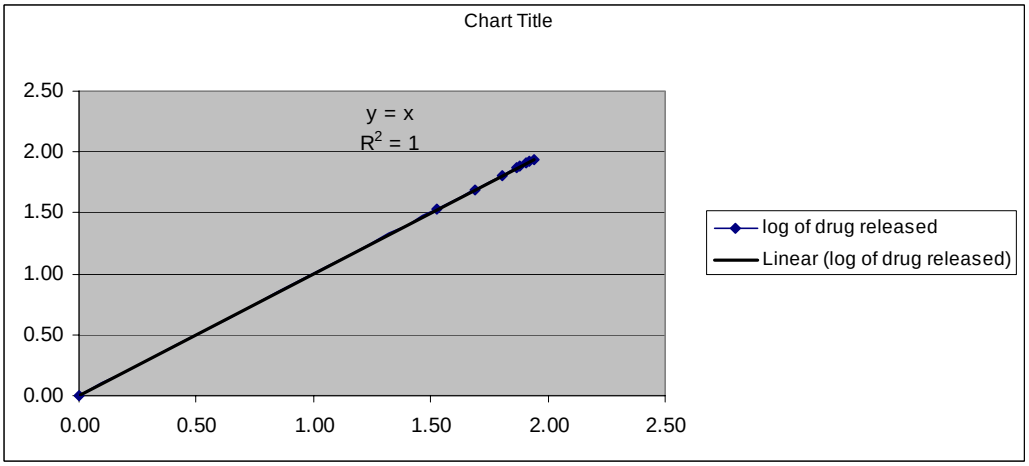


Fig : 42 Graph showing zero order kinetics of B2 buccal tablets.

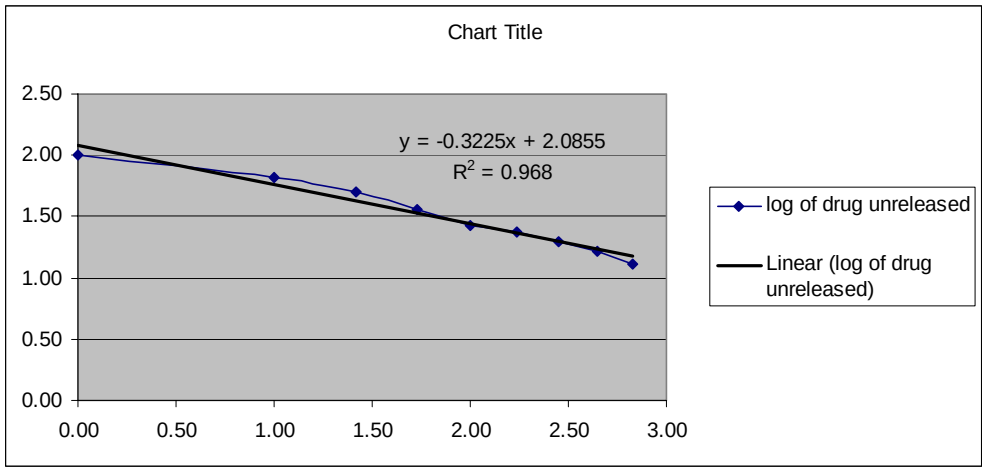


Fig : 43 Graph showing zero order kinetics of B2 buccal tablets

9.6 SWELLING STUDIES AND SWELLING INDEX

The tablets of each formulation were weighed individually (W_1) and placed separately in Petri dishes containing 2% agar gel.

At regular intervals (1h, 2h, 3h, 4h, 5h, 6h, 7h and 8h), the tablets were removed from Petri dishes and excess water removed carefully using filter paper.

Swollen tablets are reweighed (W_2), the swelling index calculated using the formula. (Table 23, Fig. 44)

Swelling Index **(S.I)** = $\mathbf{(W_1-W_2) / W_1}$

Percentage Swelling = $\mathbf{(W_1-W_2) / W_1}$ X **100**

10. RESULTS AND DISCUSSION

The aim of the present study was to develop buccal tablets, containing Nicorandil, using various bioadhesive polymers such as Carbopol 934 (CP), Polyvinylpyrrolidone (PVP), Polyvinylalcohol (PVA) and Ethylcellulose (EC), for the prolonged release of the drug nicorandil. In this work, Nicorandil is selected as an ideal drug candidate because of its potent coronary vasodilator activity. Also, it possess' the ability to hyperpolarize smooth muscle cell membrane and it is one of the emerging molecules in the treatment of hypertension and angina.

10.1 FORMULATION OF BUCCAL TABLETS

In the present study, an attempt was made to prepare different formulations of mucoretentive drug delivery system, using various bioadhesive polymers. There are two methods adapted for preparation of buccal tablets. In the first method (Table 8), the core tablet is prepared by direct compression of nicorandil, PVP, PVA and EC is coated as a backing layer [F1, F2, F3, F4, and F5] and in the second method (Table 9), various bilayered tablets were prepared using nicorandil, CP and PVP as core tablet and EC compressed over it as a backing layer [B1, B2, B3 and B4]. The prepared various tablets were made to undergo physiochemical evaluation, incompatibility studies, *in vitro* drug release and *in vitro* dissolution kinetics.

10.2 COMPATIBILITY STUDIES

The compatibility studies of the drug and the polymer and various formulations were estimated by using FT-IR [Jasco-FT-IR 8201 PC]. The IR Spectrum of the pure drug (Nicorandil-API) showed a few intense peaks at 3739.5 cm^{-1}, 1631.48 cm^{-1}, 3078.8 cm^{-1}, 3234.04 cm^{-1}, 1286.09 cm^{-1}, 999.94 cm^{-1} which were characteristic for the drug and similar peaks were observed in all tablet formulations. From the spectra, shown in the Fig. 16-24, we found that there was no significant incompatibility between the pure drug, polymer and in all nine formulations, indicating the stability of the drug in these formulations.

10.3 EVALUATION OF PHYSIOCHEMICAL PARAMETERS

Various physiochemical parameters such as thickness, weight variation, content uniformity, friability, hardness, thickness and swelling studies were studied on the prepared buccal tablets. The thickness of all the tablets fall in the range of 1.83± 0.3 to 2.42± 0.2 mm [F1, F2, F3, F4 and F5] and 2.01± 0.1 to 2.73± 0.02 [B1, B2, B3 and B4]. The readings (thickness) of all the formulations fell in the acceptable range of USP standards. The values of other parameters such as weight variation, hardness, drug content uniformity and friability are within the acceptable range. The average percentage deviation of 20 prepared buccal tablets was less than ±5%

The drug content of various buccal tablets [F1-F5 and B1-B4] ranged from 87.03-97.71%. The hardness and percentage friability of the prepared buccal tablets ranged from 6.5± 0.09 to 9.0± 0.11

kg/cm² and 0.61% to 0.13%, respectively. All the values of the physicochemical parameters are shown in Table 12.

The percentage swelling for the buccal tablets F1, F2, F3, F4 and F5 were calculated and found to be in the range of 34.5 to 49.2%, with formulation F4 showing a maximum of 49.2%. The formulations B1, B2, B3 and B4, the percentage swelling was found to be in the range of 9.4-26.7%, with formulation B3 showing maximum swelling of 26.7%. From the results of the swelling studies, the tablets did not show any appreciable change in shape and nature during the 8 h of study. The comparative percentage swelling for various prepared buccal tablets was in the order of F4> F2> F3> F1> F5 and B3> B4> B1> B2 and the data is shown Table 23 and Fig 44.

10.4 IN VITRO DISSOLUTION STUDY

The *in vitro* dissolution study of the prepared buccal tablets [nine formulations including F1, F2, F3, F4, F5, B1, B2, B3 and B4 was carried out using phosphate buffer pH 6.8 at temperature 37± 0.5ºC at 75 rpm in a dissolution apparatus (Electrolab TDT-08L. Chennai). The data of the *in vitro* release of all formulation are given in Tables 13 to 21 and the dissolution profiles are shown in Fig 25 to 33.

Among the nine formulations, F3 (Comp. : Nicorandil-3mg, CP- 100mg, PVP- 80mg and PVA- 50mg) showed maximum drug release of 80.83± 0.93% and B2 (Comp. :Nicorandil_5mg, CP_120mg, PVP_80mg) exhibited highest drug release of 87.0± 1.03%. From this dissolution studies, we found that F3 showed maximum drug release due to high wettability of the polymer PVP and PVA. The buccal tablet F5 showed lowest release of 68.17± 0.68% due to absence of PVP and PVA.

10.5 DRUG RELEASE KINETICS

The mechanism of drug release from all the nine formulations was determined using four different *in vitro* kinetic models such as first order (log cumulative percentage of drug remaining vs time), Higuchi's (cumulative percentage of drug released vs square root of time) and Kosermeyer et al's (log cumulative percentage of drug released vs log time) equations along with zero order (cumulative amount of drug released vs time) pattern. The release rate kinetics for all prepared buccal tablets is shown in Table 22. In our experiments, the *in vitro* release profiles of drug from all the formulations could be best expressed by Higuchi's equation, as the plots showed high linearity (R^2 =0.9707 to 0.9967) and the release kinetics of the best formulation (F4 and B2) were studied and the release profile are shown in Fig 36-39 and 40-43, respectively.

11. SUMMARY AND CONCLUSION

Drug delivery within the oral cavity may be summarized under buccal, sublingual and local delivery. Among the three routes of drug delivery within the oral cavity, sublingual and buccal are found to be the most effective. Here we have selected buccal drug delivery system because unlike sublingual, buccal is suitable for oral transmucosal delivery system. Buccal is a more preferred route, for the systemic transmucosal drug delivery. The reason that the buccal mucosa has an expanse of smooth muscle and relatively immobile mucosa which makes it a more desirable region for drugs used in oral mucosal drug delivery. Thus, the buccal mucosa is more filled for delivery of less permeable molecules and perhaps peptide drugs.

In this present study, nine different buccal tablets containing nicorandil, using various bioadhesive polymers such as CP, PVP, PVA and EC (backing layer), by two different methods. All the nine formulations were used for the determination of physicochemical evaluations, *in vitro* drug release and *in vitro* dissolution kinetics.

From this work, we conclude that F3 (Content: Nicorandil 3mg, CP 100mg, PVP 80mg and PVA 50mg) and B2 (Content: Nicorandil 5mg, CP 120mg, PVP 80mg) were found to be ideal buccal tablets, with the highest percentage release of 80.83± 0.93% and 87.0± 1.03%, respectively and we also found that the ideal bioadhesive carriers are PVP and PVA, because of high wettability of the mucous membrane of the buccal area. Further studies can be done to improve the buccal delivery system by *in vivo* permeation

studies. They can be employed to examine drug transport across buccal tissues from animal models. Buccal cell cultures have also been suggested as useful *in vitro* models for buccal drug permeation and metabolism. *In vivo* methods were first developed by Beckett and Triggs with buccal absorption test, with which the kinetics of drug absorption was measured. The drawbacks of this method include salivary dilution of the drug, accidental swallowing a portion of sample solution, and the inability to localize the drug solution within a specific site. Pharmacokinetic parameters such as bioavailability can then be calculated from the plasma concentration vs time profile.

The buccal mucosa offers several advantages for effective drug delivery. The mucosa is well supplied with both vascular and lymphatic drainage, first pass metabolism and in the liver and presystemic elimination in the gastrointestinal tract are avoided.

The area is well suited for a retentive device and appears to be acceptable to the patient. With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation. Buccal drug delivery is a promising area with continued research, with the aim of systemic delivery of orally inefficient drugs as well as an attractive alternative for non–invasive delivery of potent peptide and protein drug molecules. Bioadhesive studies, animal model and *in vivo* drug release could be carried out to evaluate the performance of prepared buccal tablets of Nicorandil.

REFERENCES

Agarwal V and Mishra B (1999). Design, development and biopharmaceutical properties of buccoadhesive compacts of Pentazocine. *Drug Development Industrial Pharmacy*. **25**: 701-9.

Aungst BJ and Rogers NJ (1988). Comparison of nasal, rectal, buccal, sublingual and intramuscular insulin efficacy and the effects of a bile salt absorption promoter. *Journal of Pharmacology and Experimental Therapeutics*. **24**: 23-27.

British Pharmacopeia. (2008). 2nd Edn. Medicines and Healthcare products regulatory agency (MHRA) pg.no. 3097

Camm AJ and Maltz MB (1989). A controlled single dose study of the efficacy, dose response and duration of action of nicorandil in angina pectoris. *Journal of Cardiology*. **20**: 61-65.

Choi HG and Kim CK (2000). Development of omeprazole buccal adhesive tablets with stability enhancement in human saliva. *Journal of Controlled Release*. **68**: 397-404.

Clarke's Analysis of Drugs and poisons (2004). 3rd Edn Antony C. Mattat, David Osserltonm and Bhan Widdop. Pg- 1589.

Desai KGH, Kumar TMP (2004). Development and evaluation of novel buccal adhesive core-in-cup tablets of Propanolol Hydrochloride. *Indian Journal of Pharmaceutical Sciences.* **66**: 438-443.

Edith Mathiowitz (1999). Encyclopedia of Controlled Drug Delivery. John Wiley & Sons Inc, New York. Pg: 555-557.

Frydman MA, Chapelle P, Diekmann H (1989). Pharmacokinetics of Nicorandil. *Journal of Cardiology*. **20**: 25-33.

Handbook of Pharmaceutical Excipients. 4th Ed. Royal Pharmaceutical Society of GB, London, UK. Pg : 237-241.

Hemant HA, Pather IS, Mitra AK, Thomas PJ (1999). Transmucosal Sustained Delivery of Chlorpheniramine Maleate in rabbits using a novel, natural mucoadhesive gum as an excipient in buccal tablets. *International Journal of Pharmaceutics.* **188**: 1-10.

Hessel PG, Lloyd J, Mius JG, Pass NC, Sugden GD (1989). A comparison of the availability of prochlorperazine following IM, buccal and oral administration. *International Journal of Pharmaceutic*.**. 52**: 159-164.

Higuchi T (1963). Mechanism of sustained action .Theoretical analysis of rate release of solid drugs dispersed in solid matrices. *Journal of Pharmaceutical Sciences*. **52**: 1145-1149.

Howard CA, Loyd VA. Pharmaceutical dosage forms on drug delivery systems. **7**: 202.

htpp://en.wikipedia.org/wiki/carbopol

htpp://en.wikipedia.org/wiki/polyvinylalcohol

htpp://en.wikipedia.org/wiki/polyvinylpyrolidone

Ikinci G, Sensel S, Wilson CG and Summu M (2004). Development of a buccal bioadhesive nicotine tablet formulation for smoking cessation. *International Journal of pharmaceutics.* **277**: 1173-178.

Indian Pharmacopoeia. Vol I,(1996) Delhi: The Controller of Publications; 1: 487.

Indian Pharmacopoeia.Vol II (1996) Delhi: The Controller of Publications; 1: 735-9.

Jain NK (2003). Advances in Controlled and Novel Drug Delivery-CBS Publisher and distributer, New Delhi **1**: 75-81.

Jamakandi VA, Mulla JS, Vinay BL, Shivakumar SN (2009). Formulation, characterization and evaluation of matrix type transdermal patches of a model antihypertensive drug. *Asian Journal of Pharmaceutics*. : 61-65.

Juan ML, Hilario M and Allemandi DA (2002). Double layered mucoadhesive tablets containing Nystatin. *AAPS Pharmaceutical Sciences Technology*. **3**: 3.

Kashappa G, Desai H, Pramod KM (2004). Preparation and evaluation of a novel buccal adhesive system. *AAPS Pharmaceutical Sciences and Technology*. **5**: 1-4

Kosermeyer RW, Gurny R, Peppas NA (1983). Mechanisms of solute release from porous hydrophilic polymers. *International Journal of pharmaceutics*. **15**: 25-35.

Kumar AC, Jain, Angust BJ, Adeyeye MC (2002). Development and *In-vivo* evaluation of buccal tablets prepared using danazol-sulfobutyl ether.7.b cyclodextrin. *Journal of Pharmaceutical Sciences.* **91**: 1659-1668.

Laila BH, Aksel J, Soren NR, Lona LC, Bundgard H (1992). Buccal absorption of Ketobemidone and various ester prodrugs in the rat. *International Journal of Pharmaceutics*. **88**: 243-250.

Leonetti G, Fruscio M, Gradnik R, Chianca R, Bolla GB, Prandi P, Zanchetti A (1989). Nicorandil, a new vasodialator drug , in patients with essential hypertension. *Journal of Hypertension.* **7**: 292-293.

Madgulkar A, Kadam SR, Pokharkar V (2008). Development of trilayered mucoadhesive tabletof Itraconazole with zero – order release. *Asian Journal of Pharmaceutics.***71**: 57-60.

Michel MV, Mark AL, Thomas WM and Joseph RR (1987). Prelimnary studies of oral mucosal delivery of peptide drugs. *Journal of Controlled Release.* **6**: 123-131.

Milo Gibaldi (2006), Biopharmaceutics and Clinical pharmacokinetics. 4th Ed. *Pharma Book Syndicate* : 110-142.

Mona S, Semalty A and Kumar G (2008). Formulation and characterization of mucoadhesive buccal films of Glipizide. *Indian Journal of pharmaceutical Sciences.* **70**: 43-48.

Nakhat PD, Kondawar AA, Rathi LG and Yeole PJ (2008). Development and *in vitro* evaluation of buccoadhesive tablets of Metoprolol Tartarate. *Indian Journal of Pharmaceutical Sciences.* **70:** 121-123.

Nina L, Joeben K and Andreas BS (2005). Development of a mucoadhesive and permeation enhancing buccal delivery system for PACAP. *International Journal of pharmaceutics.* **296**: 103-111.

Park CR, Munday DL (2004). Evaluation of selected polysaccharide excipients in buccoadhesive tablets for sustained release of nicotine. *Drug Dev Ind Pharm*. **30**: 609-617.

Patel, Parajapat VM, Patel BG, Patel JK (2006). Physiochemical characterization and evaluation of buccal adhesive patches containing propanolol hydrochloride. *Current Drug Delivery*. **3**: 325-331.

Paulo G, Claudia J, Elizabeth G, Massimo C, Milena S (2002). Formulation and *in vivo* evaluation of Chlorhexidine buccal tablets prepared using drug loaded chitosan microspheres. *European journal of Pharmaceutics and Biopharmaceutics*. : 233-239

Raghuram RK, Srinivas M and Srinivas R (2003). Once-Daily sustained-release matrix tablets of Nicorandil: Formulation and *in vitro* evaluation ***AAPS*** *PharmSciTech*. **4**: 1-9.

Ramana MV, Nagda C and Himaja M (2007). Design and evaluation of mucoadhesive buccal drug delivery systems containing Metoprolol Tartarate. *Indian Journal of Pharmaceutical Sciences.* **69**: 515-518.

Reinhold A and Hans P (1989). Evaluation of laminated mucoadhesive patches for buccal drug delivery. *International Journal of pharmaceutics.* **49**: 231-240.

Rowe RC, Sheskey PJ, Weller PJ (2003). Handbook of pharmaceutical excipients. London, England: American pharmaceutical association, Pharmaceutical Press. 4th Ed: 234-236

Royal Pharmaceutical Society-Martindale: The Extra Pharmacoepia, 33rd Edition (2002). UK: Royal Pharmaceutical Society : 939

Sahni J, Raj S, Ahmad SJ and Khar RK (2008). Design and *in vitro* characterisation of buccoadhesive drug delivery of Insulin. *Indian Journal of Pharmaceutical Sciences.* **1**:61-65

Sathish DK and Vincent HL (1986). Enkephalin hydrolysis in homogenates of various absorptives mucosae of the albino rabbit. *Life Sciences.* 38: 2019-2028.

Sathishbabu and Srinivasan SP (2008). Preparation and evaluation of buccoadhesive films of Atenolol. *Indian Journal of Pharmaceutical Sciences.* **70**: 175-179.

Shaila L, Subramanian G, Panday P and Udupa N (2006). Design, evaluation and pharmacokinetic study of mucoadhesive buccal tablets of Nicotine for smoking cessation. *Indian Journal of Pharmaceutical Sciences.* **68**: 829-831.

Shin SC, Jin BP, Chei JS (2000). Enhanced bioavailabiliy by buccal administration of triamcinolone acetonide from the bioadhesive gels in rabbits. *International Journal of pharmaceutics.* 37-43.

Shojari AH (1998). Buccal mucosa as a route for systemic drug delivery: A Review. *Journal of Pharmaceutical Sciences.* **1**: 15-30.

Smart JD (1991). An *in-vitro* assessment of some mucoadhesive dosage forms. *International Journal of pharmaceutics.* **73**: 69-74.

The United States Pharamacopeia. (2003). 22nd Edn. The United States Pharmacopeial convention, Inc., Pg.No 1252-1253.

Tripathi KD. Essentials of Medical Pharmacology (2003), 5th Edition. 453-454.

Varshoshaz J, Dehghan Z (2002). Development and characterization of buccoadhesive nifedipine tablets.*European Journal of Pharmaceutics and Biopharmaceutics.* **54**: 135-141.

Vijayaraghavan C, Ravi TK (2004). Buccal delivery of Nifedipine using a novel, natural muccoadhesive polymer as an excipient in buccal tablets. *Indian Drugs*. **41**: 143-148

Wong CF, Yeun KH, Peh KK (1999). Formulation and evaluation of controlled release Eudragit buccal patches. *International Journal of pharmaceutics.* **178**: 11-22.

Wong FC, Yeun KH, Peh KK (1999). Formulation and evaluation of controlled release eudragit buccal patches. *International Journal of pharmaceutics.* **178**: 11-12.