FORMULATION DEVELOPMENT AND EVALUATION OF KETOPROFEN BUCCAL TABLETS

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32

In partial fulfillment for the award of the degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

Register Number: 26111007

Under the guidance of

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Approved by Pharmacy Council of India, New Delhi, and
All India Council for Technical Education. New Delhi.

THE CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION DEVELOPMENT AND EVALUATION OF KETOPROFEN BUCCAL TABLETS"** submitted to **THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32** for the award of the degree of **Master of Pharmacy in Pharmaceutics** is a bonafide research work done by **Register Number: 26111007** under my Guidance in the Department of Pharmaceutics, C.L. Baid Metha College of Pharmacy, Chennai-600097 during the academic year 2012-2013.

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DECLARATION

I hereby declare that the thesis entitled **"FORMULATION DEVELOPMENT AND EVALUATION OF KETOPROFEN BUCCAL TABLETS"** has been originally carried out by me under the supervision and guidance of **Mr. D. Kalyanasundaram, B.Pharm., (**Industrial Guide) and **DR. R. Kumaravel Rajan, M.Pharm., Ph.D.,** (Institutional Guide) Asst. Professor, Department of Pharmaceutics, C.L.Baid Metha College of Pharmacy, Chennai-97, during the academic year 2012-2013.

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ACKNOWLEDGEMENT

I take great pleasure in acknowledging those, without whom, this work would not have been completed.

First of all, I would like to express my deep sense of gratitude to my respected guide **DR. R. Kumaravel Rajan**, **M. Pharm., Ph.D., Assistant Professor,** C. L. Baid Metha College of Pharmacy,Chennai-97 for his guidance and constant encouragement to strife better throughout the course of this investigation.

The immense help I received from my industrial guide **Mr. D. Kalyanasundaram, B.Pharm.,** cannot be discounted by any means and I would like to thank him for his valuable guidance and support in each and every aspect of the project.

The seeds of the project were long sown in my mind by **DR. Grace Rathnam M.Pharm, Ph.D**., (Principal cum HOD Dept. of Pharmaceutics) for which I thank her whole heartedly.

I would like to extend the my gratitude to **Mr. M. Lakshmanan, B.Pharm., (Managing Partner – M/s Pharmafabrikon, Madurai)**for providing the great opportunity of carrying out my project work at **Pharmafabrikon Unit-II**, **Madurai.** I would also like to thank the staff of **Pharmafabrikon Unit-II**, **Madurai** for their support and co-operation during my work there.

I thank all the Teaching and Non-teaching Staff members of **C.L. Baid Metha College of Pharmacy, Chennai-97**for their support.

I thank all my Friends, for without them this project would have not seen the light of day.

Last but not least, I acknowledge the support of my Family in every endeavour I take. No amount of gratitude can ever equal the support they have given me and for this I remain eternally in their debt.

(Reg.No.26111007)

DEDICATED
TO
MY FAMILY

ABBREVIATIONS

API	Active Pharmaceutical Ingredient
BCS	Biopharmaceutical Classification System
BP	British Pharmacopoeia
DC	Direct Compression
DSC	Differential Scanning Calorimeter
GIT	Gastro Intestinal Tract
HPMC	Hydroxy Propyl Methyl Cellulose
IP	Indian Pharmacopoeia
IPA	Isopropyl Alcohol
MCC	Micro Crystalline Cellulose
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PVP	Poly Vinyl Pyrrolidone
USP	United States Pharmacopoeia
WG	Wet Granulation

NOMENCLATURE

d_{ave}	Average diameter
C	Celsius
cm	Centimetre
°	Degree
g	Gram
h	Hour/s
Kp	Kilo pound
µm	Micro meter
µg	Microgram
mg	Milligram
ml	Millilitre
mm	Millimetre
Min	Minutes
Pa	Pascal
%	Percentage
w	Weight

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INTRODUCTION

1 Introduction

The process of drug discovery is tedious, involving a vast amount of capital expenditure, time, and man power. It is further constrained by the various rules and regulations put in place to ensure that human ethics is not compromised. This hasresulted in the decline in the number of newer molecules being introduced into the market. The checks although restrictive are necessary to avoid incidents such as the 'Thalidomide Tragedy'. Recently, many drugs, Rosiglitazone, Nimesulide (banned in the US and European Union), Valdecoxib, etc… to name a few, have been withdrawn from the market because of the severity of their adverse effects, several of which are fatal.

The decline in the development of new drug molecules can be compensated to an extent with the adoption of novel delivery systems for the drugs that are currently in the market to enhance their efficacy and lower/minimize their adverse effects.

1.1 Mucoadhesive drug delivery system

One such novel drug delivery system is the mucoadhesive drug delivery system. Investigation regarding the mucoadhesive system began in the 1980's itself[(1)]. Yet this field is still considered to be in its infancy because of the slow rate of adoption of the technology in the market and industries[(2)].

Dosage forms designed for mucoadhesive drug delivery should be small and flexible enough to be acceptable for patients and should not cause irritation. Other desired characteristics of a mucoadhesive dosage form include high drug loading capacity, controlled drug release (preferably unidirectional release), good mucoadhesive properties, smooth surface, tastelessness, and convenient application. Bio-erodible formulations containing thermoplastic polymers can be beneficial because they do not require system retrieval at the end of desired dosing interval[(2)]. A number of relevant mucoadhesive dosage forms have been developed for a variety of drugs. Several peptides, including Thyrotropin-Releasing Hormone (TRH), Insulin[(2)], Octreotide, Oeuprolide, and Oxytocin, have been delivered via the mucosal route, albeit with relatively low bioavailability (0.1–5%),owing to their hydrophilicity and large molecular weight, as well as the inherent permeation and enzymatic barriers of the mucosa.

1.2 Bioadhesion

Bio-adhesion can be defined as a state in which two components, of which one is biological in origin, are held together for extended periods of time by the help of interfacial forces. It isdenoted (esp. in pharmacy) as mucoadhesion since the main biomaterial involved is mucus present at various sites in the body[(3)].

The mechanisms involved in bio-adhesion are[(1)(4)]:

- The formation of a double-layer of electrical charge as a result of electron transfer across an interface – electronic theory .
- Fracture theory.
- Diffusion and interpenetrationpolymer chains across the interfacecan also result in adhesion.
- By means of adsorption via Van der Waals dispersion forces and hydrogen bonding – Adsorption theory.
- Wetting theoryappliesto liquid systems which present affinity to the surface in order to spread over it. This affinity can be found by using measuring techniques such as the contact angle. The general rule states that the lower the contact angle, the greater is the affinity
- Mechanical interlocking theory

All these numerous theories should be considered as supplementary processes involved in the different stages of the mucus/substrate interaction, rather than individual and alternative theories. Each and every theory is equally important to describe the mucoadhesion process. There is a possibility that there will be initial wetting of the mucin, and then diffusion of the polymer into mucin layer, thus causing the fracture in the layers to effect the adhesion or electronic transfer or simple adsorption phenomenon that finally leads to the perfect mucoadhesion[(5)].

1.2.1 Factors Affecting Mucoadhesion[(5)]

1.2.1.1 *Molecular weight*

The mucoadhesive strength of a polymer increases with molecular weights above 100,000.

1.2.1.2 *Flexibility*

It is important that the polymer chains contain a substantial degree of flexibility in order to achieve the desired entanglement with the mucus. In general, mobility and flexibility of polymers can be related to their viscosities and diffusion coefficients, as higher flexibility of a polymer causes greater diffusion into the mucus network.

1.2.1.3 *Cross-linking density*

The average pore size, average molecular weight of the cross-linked polymers, and the density of cross-linking are three important, inter-related structural parameters of a polymer network. Therefore, with increasing density of cross-linking, diffusion of water into the polymer network occurs at a lower rate which, in turn, causes an insufficient swelling of the polymer and a decreased rate of interpenetration between polymer and mucin.

1.2.1.4 *Hydrogen bonding capacity*

Bioadhesive polymers must have functional groups that are able to form hydrogen bonds, and flexibility of the polymer is important to improve this hydrogen bonding potential.

1.2.1.5 *Hydration*

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

1.2.1.6 *Charge*

Nonionic polymers appear to undergo a smaller degree of adhesion compared to anionic polymers. Strong anionic charge on the polymer is one of the required characteristics for mucoadhesion. Some cationic polymers are likely to demonstrate superior mucoadhesive properties, especially in a neutral or slightly alkaline medium. Additionally, some cationic high–molecular-weight polymers, such as chitosan, have shown to possess good adhesive properties.The pH of the membrane affects the mucoadhesion as it can influence the ionized or un-ionized forms of the polymers.

1.2.1.7 *Concentration*

If the concentration of the polymer is too low, the number of penetrating polymer chains per unit volume of the mucus is small and the interaction between polymer and mucus is unstable. In general, the more concentrated polymer would result in a longer penetrating chain length and better adhesion. However, for each polymer, there is a critical concentration, above which the polymer produces an "unperturbed" state due to a significantly coiled structure. As a result, the accessibility of the solvent to the polymer decreases, and chain penetration of the polymer is drastically reduced. Therefore, higher concentrations of polymers do not necessarily improve and, in some cases, actually diminish mucoadhesive properties.

1.2.2 Mucoadhesion sites in the body

The various sites available for mucoadhesion in the body are :

- Ocular
- Oral – GIT
- Buccal
- Nasal
- Rectal
- Vaginal

Each site of mucoadhesion has its own advantages and disadvantages along with the basic property of prolonged residence of dosage form at that particular site. In buccal and sublingual sites, there is an advantage of fast onset along with bypassing the first-pass metabolism, but these sites suffer from inconvenience because of taste and intake of food. In GIT, there is a chance for improved amount of absorption because of microvilli, but it has a drawback of acid instability and first-pass effects. Rectal and vaginal sites are the best ones for the local action of the drug but they suffer from inconvenience of administration. Nasal and ophthalmic routes have another drawback of mucociliary drainage and clearance by tears, respectively, that would clear the dosage form from the site.

1.3 Oral Mucosa

The buccal cavity is lined with mucous membrane, which is composed of stratified squamous epithelium with small mucus secreting glands[(6)]. The mucus is a thick secretion composed of water, electrolytes and several glycoproteins (large

polysaccharides bound to smaller quantities of proteins). It is adhesive in nature and helps protect the mucosa by binding with the food or other foreign particles and prevents their actual contact with the mucosa. The glycol proteins are amphoteric in nature and hence can act as a buffer for small amounts of acids and alkali. Mucus also contains bicarbonate ions which can neutralize acids[7].

The mucosa of the buccal cavity is a convenient and easily accessible site for the delivery of therapeutic agents for both local and systemic delivery as retentive dosage forms, because it has expanse of smooth muscle which is relatively immobile, abundant vascularization, rapid recovery time after exposure to stress and the near absence of Langerhans cells. Systemic drug delivery via the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to high bioavailability[8]. The principle uses of these formulations in local drug delivery within the oral cavity are for treating oro-dental problems and trigeminal neuralgia.

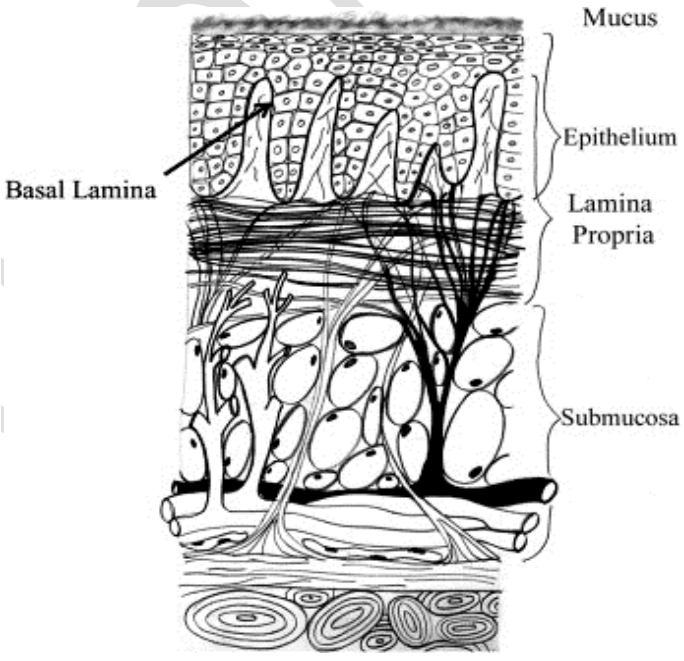


Figure 1.1: Structure of the oral mucosa[9]

1.4 Buccoadhesive Dosage Forms

The buccoadhesive dosage forms along with sub-lingual tablets, oral gels and ointments, lozenges, rapidly dissolving tablets and chewing gums are the formulations targeting drug delivery in the oral cavity[10].Other minor categories includes: drug drenched-cotton swab held it in place, either between the teeth or the cheek and gums; and a small sac containing the drug/drug formulation placed in the vestibule region near the molars.

1.4.1 The different strategies to formulate a buccoadhesive dosage forms are [4]:

a) Matrix-type delivery device: the simplest kind of delivery systems where drug is uniformly dispersed into the polymeric matrix;
b) Dosage form with an impermeable backing layer for unidirectional release of drugs;
c) Dosage form characterized by two layers from which drugs could be delivered at different release rate (fast and controlled release); and
d) A mucoadhesive dosage form with an impermeable backing layer, a polymeric matrix where drug is dispersed or dissolved and a mucoadhesive layer.

1.4.2 The different types of bioadhesive dosage forms that are designed for delivery of the drug in the buccal cavity are:

- Bioadhesive Gels
- Buccal Tablets
- Bioadhesive Solutions (Oral rinse and Sprays)[9]
- Buccal Patches and Strips[11]
- Buccoadhesive Discs
- Bio-adhesive Microspheres[9]

1.5 Buccal Tablets

The buccal tablets are formulated similar to the oral tablets but with the inclusion of a muco-adhesive polymer either of natural origin (Tragacanth, Guar gum etc...) or synthetic and semi-synthetic polymers (CarboxyMethyl Cellulose, Poly Ethylene Glycol, Polycarbophils, Hydroxyl Propyl Methyl cellulose, Poloxamer,Poly- Acrylic Acid- Hydroxyl Propyl Methylcellulose etc…)These polymers when incorporated in a formulation offer varying degrees of muco-adhesion and retention time.

Flat, elliptical or capsule-shaped tablets are usually selected for buccal tablets, since they can be most easily held between the gum and cheek. The parotid duct empties into the mouth at a point opposite the crown of the second upper molar, near the spot where buccal tablets are usually placed. This location provides the medium to dissolve the tablet and to provide for release of the medication[(12)].

The drugs, usually, presented as candidates for buccal tablets are hormones for hormonal replacement therapy, Nicotine for smoking cessation, anti-microbials for the treatment of oral infections and anti-emetics. These are all drug candidates for extended release formulations[(12)].

1.5.1 Types of buccal tablets

The different types of buccal tablets that can be fabricated are:

a) A simple mono-lithic matrix tablet
b) Matrix tablet with a water impermeable coating – unidirectional drug release
c) Matrix tablet with a backing membrane – unidirectional release
d) A bi-layered tablet with a non-adhesive drug reservoir and a mucoadhesive polymer layer
e) A bi-layered tablet with a non-bioadhesive inert layer and a drug containing bioadhesive layer.
f) A triple layered tablet- central drug containing core, upper backing membrane and a lower bioadhesive layer.

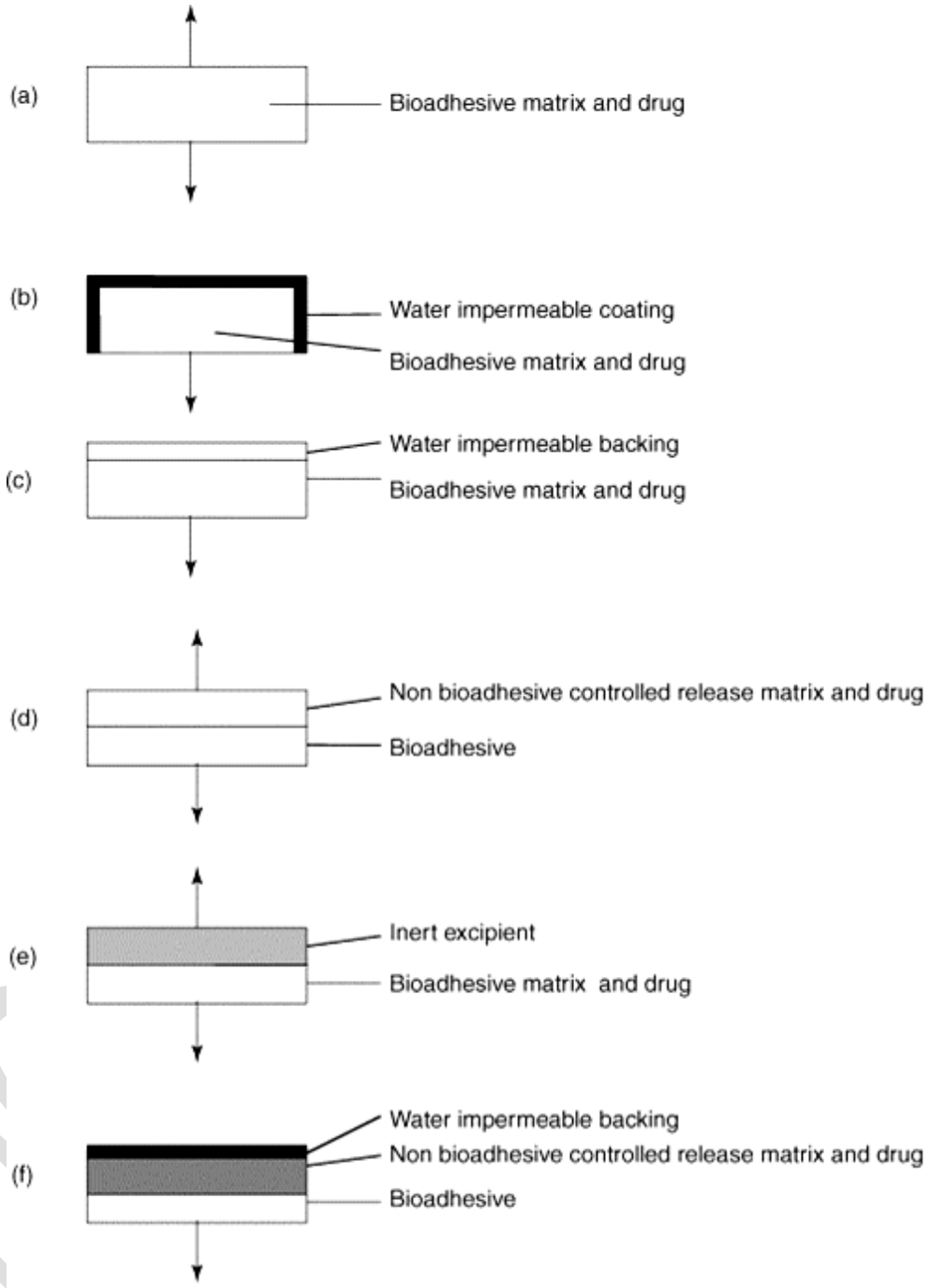


Figure 1.2: Schematic representation of different matrix tablets for buccal delivery[13]. (Arrows indicate the direction of drug release.)

The advantage of the buccal tablets over the other dosage forms is that:

- The large scale commercial preparation of these is relatively simple and economical. (compared to disc, strip and patch technology)
- They can carry a larger payload of drug.(Compared to strip or patch technology)
- Duration of drug release can be sustained longer than in the other dosage forms.
- They are convenient to use and carry around.(Compared to gel technology)

The buccal tablets are not without their share of short comings:

- Bulky when compared to the other dosage forms.
- Can be a source of discomfort to the patient. (Compared to disc or strip)
- Chances of dislodging from the site of application are relatively higher.

1.5.2 Marketed Buccal Tablets:

Table 1.1: Marketed buccal tablets

Drug	Brand	Category
Miconazole	Oravig Tab	Anti-Fungal agent
Fentanyl	Fentora Tab	Opioid Analgesic
Prochlorperazine maleate	Buccastem M Tab	D2-Antagonist

1.6 Optimization

In order to design the best formulation it is possible to use a trial and error approach, but nonetheless it is an inefficient way. Hence, systematic optimization techniques are preferable. Optimization refers to the art and science of allocating available resources to the best possible effect. Optimization techniques are used in industrial planning, allocation, scheduling, decision making etc. These methods can be divided into sequential methods, simultaneous methods or a combination of the two.

1.7 Optimization techniques in pharmaceutical industry[(14)]

The pharmaceutical industry initially used random search method (a random formulation to get a general idea of the formulation) and evolutionary technique, which involves modification of a single parameter by a predefined factor each time, until an optimum response is obtained. These methods are time consuming and costly. The optimization techniques adopted in the pharmaceutical industry are, simplex method, factorial experimental design method, and global optimization techniques.

1.7.1 Simplex method

The method involves identification of the key parameters or variables and designing the experiment such that the number of initial trial involved are n+1 (n- number of independent variables). The simplex thus formed from the initial data is used to optimize the process by moving in the direction of the desired response. This is a method of simultaneous or continuous optimization technique

1.7.2 Factorial design

The number of experiments required for this study depends upon the number of independent variables involved and the different levels at which they are studied, x^n, where, x- number of levels and n- number of independent variables. The results expressed as liner equations or interactive equations or quadratic models are fitted by carrying out multiple regression analysis and F-statistic to find statistically significant terms. This is sequential type of optimization where the experiments are completed prior to optimization work.

1.7.3 Global optimization

This method is based on the factorial method. It is better than the previous method in that it is used to find the global maxima or minima, whereas the factorial design can determine just the local maxima or minima. Hence this method requires powerful software tools for computing the complex equations generated.

1.8 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)[15]

The NSAIDs, sometimes called the aspirin-like drugs, are among the most widely used of all drugs. There are now more than 50 different NSAIDs on the global market. They provide symptomatic relief from pain and swelling in chronic joint disease such as occurs in osteo- and rheumatoid arthritis, and in more acute inflammatory conditions such as sports injuries, fractures, sprains and other soft tissue injuries. They also provide relief from postoperative, dental and menstrual pain, and from the pain of headaches and migraine. As several NSAIDs are available over the counter, they are often taken without prescription for other types of minor aches and pains. There are many different formulations available, including tablets, injections and gels. Virtually all NSAIDs, particularly the 'classic' NSAIDs, can have significant unwanted effects, especially in the elderly. Newer agents have fewer adverse actions.

1.8.1 Drug interaction: NSAIDs and Antihypertensive agents

Hypertensive patients use NSAIDs for a variety of indications. NSAIDs inhibit prostaglandin-mediated vasodilation and promote salt and water retention. Both of these mechanisms may contribute to NSAIDs partially reversing the effects of hypotensive drugs, particularly those agents whose mechanism depends on modulating prostaglandins, renin, or sodium and water balance. The dose and duration of NSAID therapy will partially determine the extent of hypotensive therapy reversal. Higher doses of NSAIDs and chronic therapy extending beyond a week will be more likely to increase BP.

This hypertensive effect of NSAIDs is a dose related problem of all classes of NSAIDs. Hence the patients on antihypertensive drugs treatment must be monitored when prescribed an NSAID concomitantly.

Hence, thereisan undeniable need for new, lower dosage NSAID formulations, with minimal/no-risk of adverse effect, that maintain efficacy comparable with that of commercially available dosages and that have a rapid onset of action.[16]

LITERATURE REVIEW

2 Literature Review

Sara Movassaghian *et al.,* [17] (2013) theorized that Amitriptyline, a tricyclic antidepressant that provides local anesthesia by blocking sodium channels, can replace topical anesthetics are widely used in dentistry. They formulated the drug as a intraoral mucoadhesive tablets assessed its efficacy in mitigating pain performing a randomized, double-blind, placebo-controlled, clinical trial on 25 healthy female volunteers. The mucoadhesive tablet was randomly placed for 15 minutes on the buccal mucogingival tissue adjacent to the root of the upper lateral incisor, and a placebo was placed on the other side. A 27-gauge needle was inserted to touch the alveolar periosteum of the designated site. The pain intensity associated with the stimulation was evaluated every 5 minutes after removing the mucoadhesive tablet using a visual analog pain scale and pain rating scoring methods. The study results concluded that the intraoral mucoadhesive Amitriptyline tablet is a promising anesthetic device for manipulating pain in dental procedures.

Anthony A. Bavry *et al.,* [18] (2011) studied chronic and non-chronic NSAIDs users among hypertensive patients. The adverse events that they monitored were all-cause death, nonfatal myocardial infarction, or nonfatal stroke. The conclusion they arrived at was that among the hypertensive patients with coronary artery disease, chronic self-reported use of NSAIDs was associated with an increased risk of adverse events during long term follow-up.

SuchadaPiriyaprasarth *et al.,* [19] (2011) investigated the effect of source variation in HPMC on the release of drug from HPMC matrix. They used a full factorial experimental design to study the *in vitro* release. The independent variables considered were the properties of HPMC from three different sources, the manufacturing process and also the drug's physiochemical properties. This study has shown that HPMC having low viscosity resulted in an increased drug release, esp. in the case of poorly soluble drugs.

GoswamiDhrubaSankar *et al.,* [20](2011)formulated a mucoadhesive tablet of Famotidine using various combinations of synthetic (HPMC-K4M, SCMC and Sodium alginate) and natural (Tragacanth and Acacia) hydrophilic polymers. The study revealed that the formulation containing HPMC K4M and its combination with Tragacanth possessed the greatest mucoadhesive strength.

Francesco Cilurzo *et al.,* [21] (2010) formulated a new mucoadhesive prolonged release tablet containing Clobetasol-17 propionate for the management of oral lichen planus. The tablets were fabricated from poly(Sodium methacrylate, Methylmethacrylate), with Hydroxyl Propyl Methyl Cellulose and $MgCl_2$. This formulation when compared to placebo and a marketed formulation, mixed extemporaneously with Orobase, resolved pain and ulceration to a significantly greater degree. The mucoadhesive tablet was better tolerated compared to the taste alteration found in the ointment formulation. Thus the effectiveness of a mucoadhesive tablet formulation of Clobetasol-17 propionate over a conventional formulation had been established.

Belgamwar V *et al.,* [22](2009) prepared mucoadhesive multiparticulate system for oral drug delivery using ionic gelation technique. The authors prepared microspheres composed of various mucoadhesive polymers including HPMC of various grades like K4M, K15M, K100M, E50LV, Carbopol of grades 971P, 974P and Polycarbophil and evaluated their mucoadhesive strength. It was observed that HPMC had greater mucoadhesive properties than Carbopol and Polycarbophil.

Ethem I. Akural *et al.,* [23] (2009) compared the efficacy and tolerance of combination of Acetaminophen and Ketoprofen with either drug alone in treating postoperative pain (surgical removal of impacted third molar). Single oral doses of Ketoprofen 100 mg + Acetaminophen 1000 mg, Ketoprofen 100 mg, Acetaminophen 1000 mg, or placebo tablets were administered to these patients and effectiveness was assessed by the onset of analgesia, pain intensity difference (PID) from baseline, sum of PID (SPID), and duration of analgesic effect. Patients were asked to rate pain intensity on the numerical scale rating (NRS) at rest and on dry swallowing. The authors measured onset of pain relief using time to PID in ≥1 category at rest or on dry swallowing (PID ≥1). The patients were also instructed to record the occurrence of adverse events and the supplemental consumption of rescue medication (Ibuprofen). The results from this study suggest that the combination of Ketoprofen 100 mg + Acetaminophen 1000 mg provided a significantly more rapid onset of analgesia than either drug given alone in the management of pain after oral surgery in this patient population. Hence, it is not possible to substitute a low dose oral Ketoprofen tablet to achieve effective pain relief.

SolimanMohammadi-Samani *et al.*,[24](2005) in their research, studied the effect of mucoadhesive polymers such as Hydroxyl Propyl Methyl Cellulose (HPMC) with viscosity grade 60 and 500 mPas, Sodium Carboxy Methyl Cellulose (NaCMC) and Carbopol 934 (Cp 934) alone or in combination with each other on the release profile of Prednisolone was studied and mucoadhesion strength of these buccoadhesive formulations was evaluated. The results showed that with different blends of HPMC viscosity grade 500 mPas or NaCMC and Cp 934 with increasing in HPMC or NaCMC/Cp 934 ratio a remarkable decrease in the rate of drug release and an appreciable increase in the mucoadhesion strength was observed. Except from the formulations prepared with HPMC viscosity grade 60 and 500 mPas, other formulation hadmore fluctuations in release profiles and their kinetics of release were not fitted to zero order model.

C. Narendra *et al.*,[25] (2005) evaluated the effect of formulation variables on release properties and bioadhesive strength in development of three layered buccal compact containing highly water-soluble drug Metoprolol Tartrate by statistical optimization technique.The three layered buccal compact comprises of a peripheral layer, a core layer and a backing layer. The peripheral polymer ratio (Carbopol 934P: HPMC 4KM) and core polymer ratio (HPMC 4KM: Na alginate) as two independent formulation variables. Four dependent variables were considered: bioadhesionforce, percentage drug release at 8h, $T_{50\%}$ and release exponent (n). The release profile data was subjected to curve fitting analysis for describing the release mechanism of MetoprololTartarate from three layered buccal compact. The main effects and interaction terms was quantitatively evaluated by quadratic model. The decrease in Metaprolol Tartrate release was observed with an increase in both the formulation variables and as the Carbopol:HPMC ratio increases the bioadhesive strength also increased. The desirability function was used to optimize the response variables and the observed responses were in agreement with the experimental values, they stated.

M.L. Vueba *et al.,* [26] (2004) studied the effects of polymer substitution and type of diluent on Ketoprofen release mechanism. The polymers studied were Methyl Cellulose, HPC and HPMC and the diluents taken were lactose monohydrate and β-cyclodextrin. The study concluded that HPMC was the one suited for designing modified release formulations of Ketoprofen and the choice of diluent used in the formulation affects its release pattern.

JafarAkbari *et al.,* [27] (2004) studied the effect of lactose (a soluble excipient) and di-Calcium phosphate(insoluble excipient) on dissolution rate, kinetic of release and adhesion force of buccal-adhesive tablets of Propranolol HCl. Each tablet composed of 80 mg Propranolol HCl, 80 mg HPMC K4M and Polycarbophil AA1 and lactose or DCP with different ratios. The results showed that the presence of the fillers increased dissolution rate of the drug and reduced the bioadhesion force. The release mechanisms from HPMC K4M were found to be diffusion and erosion.

LuanaPerioli *et al.,* [28] (2004) prepared mucoadhesive tablets using different mixture of Cellulose and Polyacrylic derivatives to obtain new formulations containing Metronidazole for periodontal disease treatment. The tablet formulations were analyzed for their swelling studies, *ex vivo* and *in vivo* mucoadhesive time, *ex vivo* mucoadhesion force, *in vitro* and *in vivo* release. The best mucoadhesive performance and the best *in vitro* drug release profile were achieved by using HydroxyEthyl Cellulose (HEC) and Carbomer 940 2:2 ratio. The chosen tablet, containing 20 mg of Metronidazole, performed 12 h drug sustained release with buccal concentrations always higher than its MIC. This study shows that a buccal tablet formulation is a feasible method of treating diseases of the oral cavity.

Mario Jug *et al.,* [29] (2004) investigated the effect of drug-cyclodextrin complexation on the buccoadhesive controlled release tablets made up of HPMC-Carbopol matrix. The drug employed was Piroxicam which is only sparingly water soluble. The complexation with Hydroxypropyl-β-Cyclodextrin resulted in higher solubility due to the higher water uptake by the polymer. The complex also increased the diffusivity of the drug through the membrane (*in vitro*). The inclusion of hydrophilic polymers can increase the drug solubility and its permeation.

H.YeşimKarasulu *et al.,* [30] (2004) developed a more effective treatment for vaginal candidasis, by formulating ketoconazole in a bioadhesive tablet formulations that increased the time of contact of drug with the vaginal mucosa. The bioadhesive vaginal tablets were prepared by direct compression of sodium Carboxy Methyl Cellulose or Poly Vinyl Pyrrolidone or Hydroxy Propyl Methyl cellulose (HPMC E50) with Ketoconazole. The dissolution studies of bioadhesive tablets and commercial ovules were carried out and a good sustained release action was obtained with bioadhesive tablets containing 1:1 and 1:2 drug/polymer ratio using HPMC E50. These bioadhesive tablets containing 400 mg of KTZ showed a zero-order drug release kinetic.

Donald R. Mehlisch[31](2002)presented his review on post-operative dental pain management. He stated that an experience of poorly managed pain related to dental treatment can lead patients to avoid or postpone treatment. NSAIDs have been the traditional treatment for moderate pain and inflammation. NSAIDs such as Ibuprofen, Ketorolac, Flurbiprofen, Ketoprofen, Diclofenac, Aspirin and Aspirin derivatives diminish postoperative hyperalgesia peripherally. He concludes that the use of combinations of NSAIDs and or centrally acting analgesics is a better approach compared to the use of a single agent, which gives rise to adverse reactions.

DesiderioPassàli *et al.,* [32](2001)compared the efficacy and tolerability of mouthwash formulations of Ketoprofen lysine salt, an anti-inflammatory agent, and Benzydamine hydrochloride, a local anesthetic, in patients with acute inflammation of the pharyngeal cavity. It was observed that Ketoprofen lysine salt mouthwash exerts a significantly longer first-application analgesic action with significantly greater local tolerability than Benzydamine hydrochloride in patients with pharyngeal pain of inflammatory and/or infectious origin.

RadkoKomers *et al.,* [33] (2001) investigated the risk of congestive heart failure associated with combined use of diuretics and NSAIDs in patients older than 55years. The use of NSAIDs concomitantly with diuretics is known to exacerbate the existing CHF condition in the patients. The study concluded that the simultaneous use of the above two classes of drugs increased the risk of hospitalization for CHF by as much as 2-fold, especially in those with an existing serious CHF.

Gary E. Ruoff[34](1998) has reviewed that an estimated 25% of the overall population of the United States and 55% to 60% of the population aged 65 to 74 years are hypertensive. Many patients with hypertension also take NSAIDs, the most commonly prescribed analgesic medications in the United States. It is estimated that as many as 20 million patients and 12% of the population aged ≥60 years are taking concurrent NSAIDs and antihypertensive medication. This overlap is significant, because NSAIDs inhibit eicosanoid synthesis and can thus limit the effectiveness of antihypertensive drugs that exert all or part of their blood pressure—lowering action through the stimulation of eicosanoid synthesis or release. Overviews of clinical trial data indicate that the blood pressure of patients with controlled hypertension can be raised by 3 to 6 mm Hg during concurrent treatment with NSAIDs, which can produce a significant increase in subsequent stroke, end-stage renal disease, or congestive heart failure. Since, the incidence of these adverse events increases age, the use of NSAIDs in the elderly and the risk category patients must be monitored or else alternative drugs such as Tramadol or Acetaminophen must be used.

P Minghetti *et al.,*[35] (1998) experimented on buccoadhesive formulations of Acitretin, an aromatic retinoid used in the treatment of buccal keratinization disorders.Ten different formulations of two-layer buccoadhesive tablets were considered. They formulated ten different formulations of two-layer buccoadhesive tablets where Carbopol 934P:HPMC K4M, 1:2 ratio, formed the lower buccoadhesive layer and HPMC matrix (different grades) formed the rate controlling polymer in the upper layer. Lactose was used as the diluent. The authors observed that a high concentration of HPMC (viscosity grade E5) produced a prolonged drug release compared to that of a low concentration formulation.

Rajesh Khanna *et al.,*[36] (1996) formulated buccoadhesive erodible tablets for local delivery of Clotrimazole to the oral cavity using different bio-adhesive polymers along with soluble excipients like mannitol and Poly Ethylene Glycol-6000. The *in vitro* adhesion time and release characteristics were found to be a function of the type of polymer and also the total composition of the tablets. The study revealed that the bioadhesive polymers in conjugation with the other excipients dictated the adhesive property and release property of the tablets

BuketTaylan *et al.,* [37](1996) experimented with sustained release cum buccoadhesive tablet formulation using HPMC and Polycarbophil. The release from a single dose HPMC matrix as compared to a conventional dosage form revealed a smoother plasma drug profile for the former. Thus HPMC is suitable for the sustained release of the drug from the tablet although the API used, Propranolol caused oral ulcers.

A.P. Sam *et al.,* [38](1992) evaluated the mucoadhesive property of various film forming and non-film forming polymers using Wilhelmy plate method. The experimental results showed that the mucoadhesive property of the polymers are in the following ranking : CMC > HPMC K100M > HPMCP > Polycarbophil> HPMC K4M > Amylopectin > Eudragit RS 100. The strength of mucoadhesion also depended on the surface area of the polymer submerged in the mucus.

P. Giunchedi *et al.,* [39] (1991) designed a pulsatile dosage form of Ketoprofen using tablet in capsule technique. Their rationale was that diseases like rheumatoid disorders are influenced by circadian rhythms. Hence, a mere extended release dosage form would not be an optimum choice, they concluded. The drug was formulated as a 'multiple-unit' dosage form, consisting of four hydrophilic matrices made of HPMC, placed in a hard gelatin capsule. The study results showed that the dosage form had a pulsatile profile as evidenced from the spike in the plasma drug concentration after the 2^{nd} and 8^{th} hour of administration. Thus an existing drug can serve better when formulated appropriately.

D.A. Henry[40](1988) reviewed that the adverse reaction to NSAIDs based on their pharmacological actions. NSAIDs precipitate renal syndromes, of which functional renal impairment is the most important. This may precipitate cardiac failure, and hyperkalaemia is an additional hazard. Antagonism of the action of diuretics may contribute to the fluid retention, and antagonism of antihypertensive therapy is probably quite common and may result in additional unnecessary therapy. He proposed that patients at risk of functional renal impairment from NSAIDs can be identified readily and in these subjects the drugs have to be used with great care and with appropriate monitoring.

A.G. Eshra *et al.*,[41] (1988) studied the influence of milk and of a standard breakfast on Ketoprofen bioavailability from commercial capsules (50 mg). The drug was administered as a single oral dose. They evaluated the absorption rate by means of urinary excretion measurements and the drug urine concentrations were determined by HPLC. The data were then statistically analyzed by the t-test for paired observations. It was found that milk significantly reduced the extent of Ketoprofen absorption, while both the rate and extent of absorption were significantly reduced by food. This shows that the justification of taking NSAIDs along with food to reduce their gastric tract injury can lead to reduced bio-availability and delayed onset of action.

AIM & OBJECTIVES

3 Aim and Objectives

The aim of the present investigation was to formulate Ketoprofen buccal tablets containing 12.5mg, with a thickness of about 2mm and a diameter less than 4mm. Ketoprofen is a Non- Steroidal Anti-Inflammatory Drug, prescribed for the treatment of rheumatoid arthritis, osteo-arthritis and dental pain & inflammation. In general, Ketoprofen falls under BCS – class II (low solubility / high permeability), but pH dependent solubility behavior of Ketoprofen is used as the concept of designing buccal dosage form in present investigation, since the dose number of Ketoprofen is 0.00529.

Therefore the objective of the formulation includes:

Preparation of various formulations of Ketoprofen buccal tablets, using various grade of HPMC (K4M, K100 and E50) and different granulation technique for the manufacturing process, based on a 2^4-full Factorial design was the primary objective. Determination of the *in vitro* drug release profile and swelling index of the Ketoprofen buccal tablets was also included in the study. The buccoadhesive property and the *ex vivo* drug permeation for the various formulations are to be evaluated. Compiling the data in an optimization-software and analyzing the effect of different independent variables on the various responses is also the part of the investigation. The performance of evaluations, on the finished product dosage form of Ketoprofen buccal tablets, like weight variation, friability, hardness, and thickness, are to be included in the study. In order to determine the drug release kinetics, the *ex vivo* drug release data is to be fitted into the various kinetic models.

PLAN OF WORK

4 Plan of Work

The present study focused on the formulation of buccal tablets of Ketoprofen for use in mitigating pain and inflammation in the oral cavity.

4.1 Flow of work

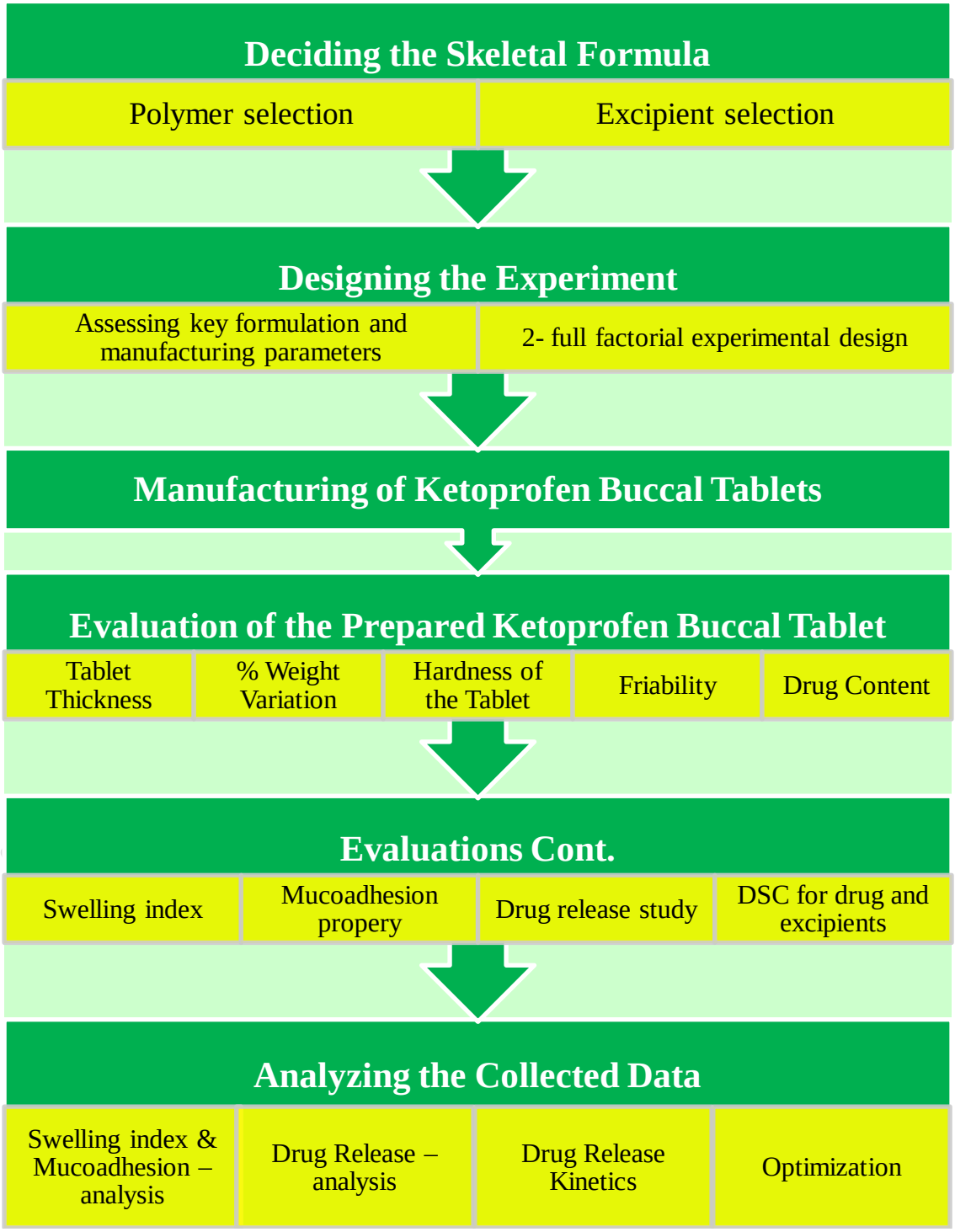


Figure 4.1: Schematics of plan of work

DRUG & EXCIPIENT PROFILES

5 Drug and Excipient Profile

5.1 Ketoprofen[42]

5.1.1 Official

USP, BP, IP

5.1.2 Chemical name and CAS number

2-(3-benzoylphenyl)-propionic acid; 89796-99-6

5.1.3 Molecular formula and molecular weight

$C_{16}H_{14}O_3$; 254.29

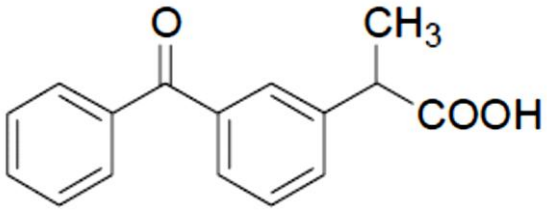
5.1.4 Melting point

≈95°C

5.1.5 Origin of substance

Synthetic

5.1.6 Structure



5.1.7 Category

Non-Steroidal Anti-Inflammatory Drug

5.1.8 Solubility

It is freely soluble in ethanol, chloroform, acetone, ether; soluble ib benzene and strong alkali but practically insoluble in water @ 20°C,

5.1.9 Proprietary names

Actron, Nexcede, Orudis, Orudis KT, Oruvail, Apo-Keto

5.1.10 Clinical Pharmacology

It is a racemate with only the S-enantiomer possessing activity.

5.1.11 Mechanism of action

It inhibits the prostaglandin and leukotriene synthesis

It has an antibradykinin activity as well as lysosomal membrane stabilizing action

5.1.12 Pharmacokinetics

- ***Absorption***

Ketoprofen is rapidly and well absorbed after oral administration. Peak plasma concentrations are reached approximately 0.5-2 hours after an oral dose. The presence of food slows the absorption.

- ***Distribution***

Aceclofenac is highly protein bound (>99%). The volume of distribution is approximately 0.1L/kg.

- ***Metabolism***

Ketoprofen is metabolized by way of conjugation to the glucuronic acid. But since the metabolite is unstable it reverts back to the parent compound. Thus the conjugate serves as a reservoir for the drug. There are no known active metabolite for Ketoprofen

- ***Excretion***

Renal excretion is the main route of elimination, with ~80% of the administered dose excreted within 24h of administration. The plasma elimination half-life of the drug is approximately 2.05±0.58 h.

5.1.13 Indications

Ketoprofen is indicated in Rheumatoid arthritis and osteo-arthritis, dysmenorrhea, and post-operative pain.

5.1.14 Doseage

50-75mg every 4 hours

5.1.15 Contraindications

Ketoprofen should not be administered to patients hypersensitive to Ketoprofen or other NSAID's, or patients with history of Aspirin or NSAID's related allergic and to patients with anaphylactic reactions or with peptic ulcers or GI bleeding, moderate or severe renal or hepatic impairment.

5.1.16 Adverse effects

The most common side effects are rash, ringing in the ears, headache, dizziness, drowsiness, abdominal pain, nausea, diarrhea, constipation, heartburn, retention of fluid, and shortness of breath. Serious side effects are rare and mostly result from gastrointestinal (GI) damage.

5.1.17 Drug interactions

Drug interactions associated with Ketoprofen are similar to those observed with other NSAID's. It interacts with the anti-hypertensive drugs other than Calcium channel blockers by reducing their efficacy.

5.2 Excipient Profile

5.2.1 Hypromellose[43]

5.2.1.1 *Nonproprietary names*

BP: Hypromellose; USP: Hypromellose

JP: Hypromellose; PhEur: Hypromellose

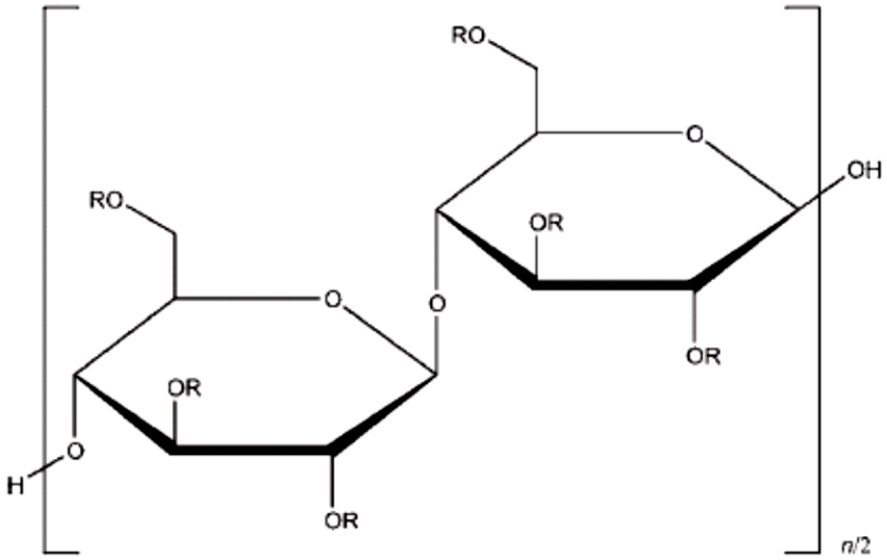
5.2.1.2 *Synonyms*

Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; hypromellosum; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; MHPC; Pharmacoat; Tylopur; Tylose MO.

5.2.1.3 *Chemical name and CAS Registry Number*

Cellulose hydroxypropyl methyl ether [9004-65-3]

5.2.1.4 *Chemical Structure*



where R is

H, CH_3, or $CH_3CH(OH)CH_2$

5.2.1.5 *Applications in Pharmaceutical Formulation*

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations.

Table 4.1: Application of HPMC at various concentrations

Dosage Form	Concentration	Application
Tablets	2-5% w/w	Binder
	10-80% w/w (High Viscosity grades)	Matrix- XR Formulations
	2-20% w/w	Film Coating
Liquids	0.25-5.0% w/w	Suspending/Thickening Agents

In addition, it is used as bioadhesive or mucoadhesive material in various types of formulations. In topical formulations, as an emulsifying, suspending and stabilizing agent.

5.2.1.6 ***Properties of Hypermellose***

Table 4.2: Properties of HPMC

Acidity/alkalinity	pH 5.0–8.0 for a 2% w/w aq. Solution
Ash	≤1.5%
Auto-ignition Temperature	360°C
Density	0.341 g/cm^3, Bulk
	0.557 g/cm^3, Tapped
	1.326 g/cm^3, True
Melting Point	190–200°C. (Browns)
	225–230°C. (chars)
	170–180°C. (Glass Transition Temperature)
Moisture Content	Hygroscopic-Depends on the relative humidity of the surrounding
Specific Gravity	1.26
Solubility	Soluble in cold water. Insoluble in hot-water, ethanol, ether

5.2.1.7 *Grades of Hypermellose*

Table 4.3: HPMC viscosity grades

Hypromellose Products	Pharmacopoeial Designation	Viscosity @ 2%w/v Aq. Solution (mPas)
Methocel K100	2208	100
Methocel K4M	2208	4000
Methocel E50	2910	50

5.2.1.8 *Stability and Storage Conditions*

Solutions are stable at pH 3–11. It is temperature sensitive, gelation occurs at 50 - 90^{o}C Aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

5.2.1.9 *Incompatibilities*

Hypromellose is incompatible with some oxidizing agents.

5.2.2 Microcrystalline Cellulose[43]

5.2.2.1 *Nonproprietary Names*

BP: Microcrystalline cellulose; JP: Microcrystalline cellulose

PhEur: Cellulosummicrocristallinum; USP-NF: Microcrystalline cellulose

5.2.2.2 *Synonyms*

Avicel PH, Celex, cellulose gel, Celphere, Ceolus KG, Crystalline Cellulose, E460, Emcocel, Ethispheres, Fibrocel, Pharmacel, Tabulose, Vivapur.

5.2.2.3 *Chemical Name and CAS Registry Number*

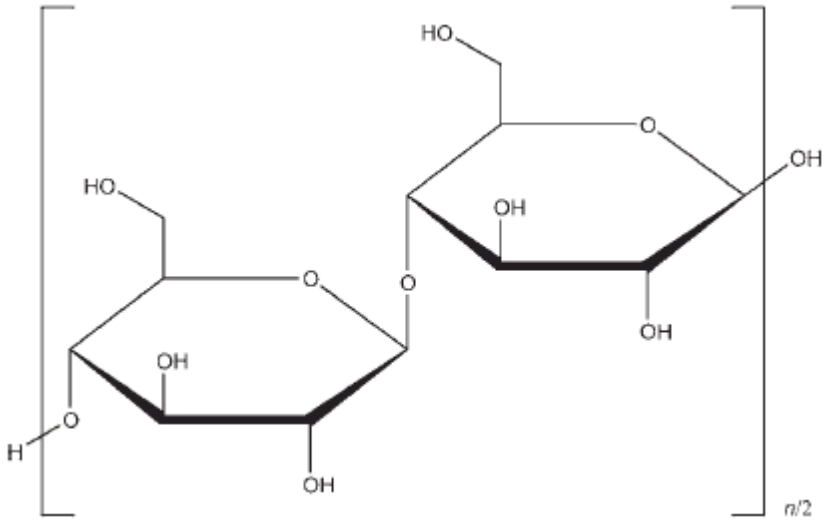
Cellulose [9004-34-6]

5.2.2.4 *Empirical Formula and Molecular Weight*

$(C_6H_{10}O_5)_n$; Mol. Wt. ≈36 000

where n ≈ 220.

5.2.2.5 *Structural Formula*



5.2.2.6 *Functional Category*

Adsorbent, Suspending agent, Tablet and Capsule diluent, Tablet disintegrant.

5.2.2.7 *Applications in Pharmaceutical Formulation*

It is used as a binder/diluent in oral tablet and capsule formulation in both wet-granulation and direct-compression processes. It also has some lubricant(8) and disintegrant properties that make it useful in tableting

Table 4.4: Applications of MCC at different concentrations

Use	Concentration (%)
Adsorbent	20–90
Anti-adherent	5–20
Capsule binder/diluent	20–90
Tablet disintegrant	5–15
Tablet binder/diluent	20–90

5.2.2.8 *Properties of Avicel PH 112*

Table 4.5: Properties of MCC PH 112

Grade	Nominal Mean Particle Size(µm)	Particle Size Analysis		Moisture Content (%)
		Mesh Size	Percentage Retained	
Avicel PH-112	100	60	≤8	≤1.5

5.2.2.9 *Stability and Storage Conditions*

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

5.2.2.10 *Incompatibilities*

Microcrystalline cellulose is incompatible with strong oxidizing agents.

5.2.3 Povidone[43]

5.2.3.1 *Nonproprietary Names*

BP: Povidone; JP: Povidone

PhEur: Povidone; USP: Povidone

5.2.3.2 *Synonyms*

E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; povidonum; Povipharm; PVP; 1-vinyl-2-pyrrolidinone polymer.

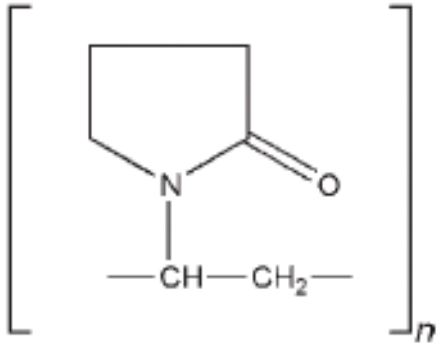
5.2.3.3 *Chemical Name and CAS Registry Number*

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

5.2.3.4 *Empirical Formula and Molecular Weight*

Povidone K 90 -1 000 000 (approx.)

5.2.3.5 *Chemical Structure*



5.2.3.6 *Functional Category*

Disintegrant; dissolution enhancer; suspending agent; tablet binder

5.2.3.7 *Applications in Pharmaceutical Formulations*

Table 4.6: Pharmaceutical applications of PVP

Use	Concentration (%)
Carrier for drugs	10–25
Dispersing agent	Up to 5
Eye Drops (solubilizer)	2–10
Suspending agent	Up to 5
Tablet (binder, diluent or coating agent)	0.5–5

5.2.3.8 *Physical Properties*

Table 4.7: Physical properties of PVP

Acidity/alkalinity	**pH= 4.0-7.0 (5% aq. solution PVP K 90)**
Density	0.29–0.39 g/cm3 (bulk)
	0.39–0.54 g/cm3 (tapped)
	1.18 g/cm3 (true)
Melting point	Softens at 150°C.
Moisture content	Very hygroscopic. Depends on the relative humudity of the environment
Particle size distribution - PVP K90	90% >200µm; 95% > 250µm
Solubility	Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K-value
Viscosity PVP K90 (5% solution @ 25°C	Ethanol (95%): 53.0 mPas; Propanol: 90.0 mPas

5.2.3.9 *Stability and Storage Conditions*

Povidone darkens to some extent on heating at 1508C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–1308C; steam sterilization of an aqueous solution does not alter its properties. Aqueous solutions are susceptible to mold growth and consequently require the addition of suitable preservatives.

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

5.2.3.10*Incompatibilities*

Povidone is generally compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. However, it forms molecular adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds.

5.2.4 Magnesium stearate[43]

5.2.4.1 *Non-proprietary Names*

BP: Magnesium stearate; JP: Magnesium stearate

PhEur: Magnesiistearas; USPNF: Magnesium stearate

5.2.4.2 *Synonyms*

Magnesium octadecanoate, octadecanoic acid magnesium salt and stearic acid magnesium salt.

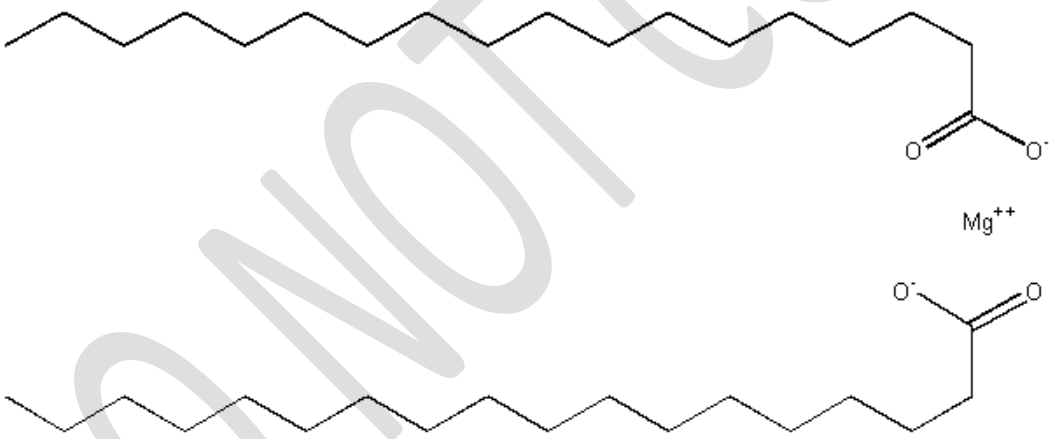
5.2.4.3 *Chemical Name*

Octadecanoic acid magnesium salt

5.2.4.4 *Empirical Formula and Molecular Weight*

$[CH_3 (CH_2)_{16}COO]_2 Mg$; Mol.Wt. = 591.34

5.2.4.5 *Chemical Structure*



5.2.4.6 *Physical Properties*

Melting point - 117-150˚C

Solubility - It is practically insoluble in ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

5.2.4.7 *Functional Category*

Tablet and capsule lubricant.

5.2.4.8 *Applications in Pharmaceutical Formulations*

It is widely used in cosmetics, foods and pharmaceutical formulations. It is primarily used as a lubricant in the manufacturing of tablets and capsules, in the concentration of 0.25-5.0%. It is also used in barrier creams.

5.2.4.9 ***Stability and Storage Conditions***

It should be stored in a well closed container in a cool, dry place.

5.2.4.10***Incompatibilities***

It is incompatible with strong oxidizing agents, strong acids, alkalis and iron salts. It cannot be used in products containing aspirin, some vitamins and most alkaloidal salts.

5.2.5 Isopropyl Alcohol[43]

5.2.5.1 *Nonproprietary Names*

BP: Isopropyl Alcohol; JP: Isopropanol

PhEur: Isopropyl Alcohol; USP: Isopropyl Alcohol

5.2.5.2 *Synonyms*

Alcohol isopropylicus; dimethyl carbinol; IPA; isopropanol; petrohol; 2-propanol; sec-propyl alcohol; rubbing alcohol.

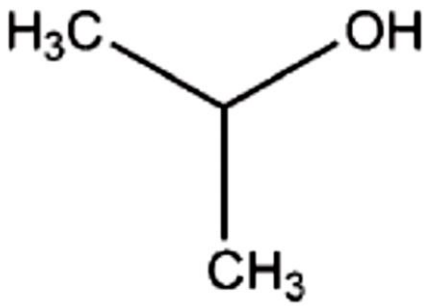
5.2.5.3 *Chemical Name and CAS Registry Number*

Propan-2-ol [67-63-0]

5.2.5.4 *Empirical Formula and Molecular Weight*

C_3H_8O; 60.1

5.2.5.5 *Structural Formula*



5.2.5.6 *Functional Category*

Disinfectant; solvent.

5.2.5.7 *Applications in Pharmaceutical Formulation*

Isopropyl alcohol is used as a solvent both for tablet film-coating and for tablet granulation,where the isopropyl alcohol is subsequently removed by evaporation. Its primary use, though, is as a solvent in topical formulations.

5.2.5.8 ***Properties***

Table 4.8: Properties of IPA

Antimicrobial activity	**Isopropyl alcohol is bactericidal @ >70% v/v**
Autoignition temperature	425°C
Boiling point	82.4°C
Dielectric constant D^{20}	18.62
Flammability	Flammable.
Freezing point	-89.5°C
Melting point	-88.5°C
Moisture content	0.1–13% w/w for commercial grades
Refractive index	$n^{20}{}_D$= 1.3776; $n^{20}{}_D$= 1.3749
Solubility	Miscible with benzene, chloroform, ethanol (95%), ether, glycerin, and water. Soluble in acetone; insoluble in salt solution
Specific-gravity	0.786
Vapor density(relative)	2.07 (air = 1)
Vapor-pressure	133.3 Pa (1 mmHg) at - 26.1°C;
	4.32 kPa (32.4 mmHg) at 20°C;
	5.33 kPa (40 mmHg) at 23.8°C;
	13.33 kPa (100 mmHg) at 39.5°C.
Viscosity(dynamic)	2.43 mPas@20°C

5.2.5.9 ***Stability and Storage Conditions***

Isopropyl alcohol should be stored in an airtight container in a cool, dry place.

5.2.5.10*Incompatibilities*

Incompatible with oxidizing agents such as hydrogen peroxide and nitric acid, which cause decomposition. Isopropyl alcohol may be salted out from aqueous mixtures by the addition of sodium chloride, sodium sulfate, and other salts, or by the addition of sodium hydroxide.

MATERIALS & METHODOLOGY

6 Materials and Methodology

6.1 *Materials and Equipments*

6.1.1 Materials

Table 4.9: List of materials and their application in the formulation

S.no.	Materials	Manufacturers/Suppliers	Application
1	**Ketoprofen IP**	PharmaFabrikon, India	API
2	**Methocel K4M (HPMC)**	Dow Wolff Cellulosics, Germany	Buccoadhesive Polymer
3	**Methocel K100 (HPMC)**	Dow Wolff Cellulosics, Germany	Buccoadhesive Polymer
4	**Methocel E50 (HPMC)**	Dow Wolff Cellulosics, Germany	Buccoadhesive Polymer
5	**Plasdone K 90 (PVP)**	ISP Pharmaceuticals, USA	Binder
6	**Avicel PH 112 (MCC)**	FMC Biopolymer, USA	Filler
7	**Magnesium Stearate**	PharmaFabrikon, India	Glidant
8	**Isopropyl Alcohol (IPA)**	PharmaFabrikon, India	Solvent

6.1.2 Instruments and Equipment

Table 4.10: List of instruments and equipments

S.no.	Instruments/Equipment	Manufacturer
1	Digital Balance	Infra, India
2	Sieve no. 16	SECOR, India
3	Sieve no. 20	SECOR, India
4	Sieve no. 30	SECOR, India
5	6 Station Rotary Compression Machine	Accura Punching Machine
6	Vernier Calipers	Gogna, India
7	Analytical Digital Balance	Mettler Toledo, Germany
8	Hardness Tester	Dr.SchleunigerPharmatron, Switzerland
9	Friability Tester	Electrolab, India
10	Disintegration Apparatus	Electrolab, India
11	Dissolution Apparatus	Electrolab, India
12	Franz Diffusion Cell	Orchid Scientifics, India
13	Magnetic Stirrer / Heating Unit	REMI, India
14	UV Visible Spectro Photometer	Shimadzu, Japan

6.2 Methodology

6.2.1 Design of Experiment

The important formulation factors identified were the concentrations of:

- concentration of HPMC K4M,
- concentration of HPMC K100,
- concentration of HPMC E50, and
- the methods of manufacture – wet granulation (non-aqueous) and direction compression.

Taking these as the independent variable, the experiment was designed as a 2-level full Factorial. (2^n – where, n is the number of independent variables)

Table 4.11: Levels of Independent Variables

Independent Variables	Low Level	High Level
% HPMC K4M	5	20
% HPMC K100	10	40
% HPMC E50	5	20
Method of Manufacture	Direct Compression	Wet Granulation

Table 4.12: Experimental design based on key parameters

S.no:	Factor 1: Manufacturing Process	Factor 2: % HPMC K4M	Factor 3: % HPMC K100	Factor 4: % HPMC E50
1	DC	5	10	5
2	DC	5	10	20
3	DC	5	40	5
4	DC	5	40	20
5	DC	20	10	5
6	DC	20	10	20
7	DC	20	40	5
8	DC	20	40	20
9	WG	5	10	5
10	WG	5	10	20
11	WG	5	40	5
12	WG	5	40	20
13	WG	20	10	5
14	WG	20	10	20
15	WG	20	40	5
16	WG	20	40	20

6.2.2 Pre-compressional Studies

Ketoprofen and the polymers provided by the industry were subject to DSC analysis.

Ketoprofen was further assayed by titrimetric analysis[42]. Ketoprofen was then subject to particle size analysis by sieve method[42] and its solubility in pH 6.8 was determined by equilibrium method.

6.2.3 Formulation of Ketoprofen Buccal Tablets

The formulations were prepared according to a predefined random order so as to nullify the extemporaneous effects such as time, environmental temperature, humidity etc…

6.2.3.1 *Formulations prepared by dry granulation method*

Table 4.13: Formulations prepared by direct compression method

MANUFACTURING PROCESS	DIRECT COMPRESSION							
STANDARD ORDER	1	2	3	4	5	6	7	8
FORMULATION CODE	DC.5.10.5	DC.5.10.20	DC.5.40.5	DC.5.40.20	DC.20.10.5	DC.20.10.20	DC.20.40.5	DC.20.40.20
KETOPRFEN	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
HPMC K4M	0.63	0.63	0.63	0.63	2.5	2.5	2.5	2.5
HPMC K100	1.25	1.25	5	5	1.25	1.25	5	5
HPMC E50	0.63	2.5	0.63	2.5	0.63	2.5	0.63	2.5
MG STEARATE	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
MCC PH 112	51.49	49.62	47.74	45.87	49.62	47.75	45.87	44

Note: All quantities in milligram

- The ingredients weighed out for 2000 tablets.
- Ketoprofen, Magnesium stearate, HPMC K4M, HPMC K100, and HPMC E50 were then sieved using sieve no. 30.
- The MCC PH 112 was sieved separately using sieve no. 16.
- The two were then hand mixed thoroughly.
- The blended powders were then compacted using a 6 station punching machine using 7/32 punch tooling with an average weight of 70 mg per tablet.

6.2.3.2 *Formulations prepared by wet granulation (non-aqueous) method*

Table 4.14: Formulations prepared by wet granulation method

MANUFACTURING PROCESS	WET GRANULATION							
STANDARD ORDER	9	10	11	12	13	14	15	16
FORMULATION CODE	WG.5.10.5	WG.5.10.20	WG.5.40.5	WG.5.40.20	WG.20.10.5	WG.20.10.20	WG.20.40.5	WG.20.40.20
KETOPRFEN	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
HPMC K4M	0.63	0.63	0.63	0.63	2.5	2.5	2.5	2.5
HPMC K100	1.25	1.25	5	5	1.25	1.25	5	5
HPMC E50	0.63	2.5	0.63	2.5	0.63	2.5	0.63	2.5
MG STEARATE	3	3	3	3	3	3	3	3
PVP K 90	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8
MCC PH 112	49.19	47.32	45.44	43.57	47.32	45.45	43.57	41.7
IPA	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Note: All powder quantities in milligram
IPA measured in milliliter

- The ingredients were weighed out for 2000 tablets.
- All the ingredients except Magnesium stearate, HPMC E50, PVP K90 and IPA were sieved and hand mixed together.
- Then PVP K 90 was dissolved in sufficient quantity of IPA was added slowly in small quantities to the previous blend and it was hand mixed thoroughly.
- The wet mass was air dried to remove the IPA.
- The dried mass was then passed through sieve no. 30 to obtain granules.
- To the above obtained granules, HPMC E50 and Magnesium Stearate were added and mixed well.
- The granular mixture was then compacted using a 6 station punching machine using 7/32 punch tooling with an average weight of 70 mg per tablet.

6.2.4 Ketoprofen – Buccal Tablet Evaluations

6.2.4.1 *Uniformity of Weight*

Twenty tablets were selected at a random and weighed individually. The average weight was calculated. The percentage deviation of tablets was calculated and compared with the standard specifications.

Table 4.15: Limits for Tablet Weight Variation

S.no	Average weight of a tablets	% Deviation
1	80 mg or less	±10
2	80-250 mg	±7.5
3	More than 250mg	±5

6.2.4.2 *Thickness*

The thickness was measured to determine the uniformity of size and shape. Thickness of the Ketoprofen buccal tablets was measured using vernier caliper.

6.2.4.3 *Hardness*

Hardness is defined as the force required for breaking a tablet at diametric compression test and it is termed as tablet crushing strength. Hardness of the prepared formulations was determined using a tablet hardness tester. It was expressed in kp.

6.2.4.4 *Friability*

Friability of the prepared formulations was determined by using a friability tester. Pre- weighed sample of tablets was placed in the friability tester, which was then operated for 25 revolutions for 4 min, tablets were dusted and reweighed. The friability of the tablets was calculated using the formula mentioned below.

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight of the tablets}}{\text{Initial weight of the tablets}} \times 100$$

Equation 1

6.2.4.5 *Drug Content*

Ten tablets were randomly taken, weighed and powdered. The powder weight equivalent to 140mg of Ketoprofen was weighed out and put in 150ml of methanol and placed in an ultra sonicator for 5 min. The sonicated solution was then filtered out using a Whatman No. 1 filter paper. The filtered solution was then made-up to 250ml using methanol. 5ml from the above solution was taken and diluted to 100ml with methanol. The final solution was analyzed using U.V. Visible spectrophotometer at 258nm. The drug content was computed from the A (1%, 1cm) (662.0, for Ketoprofen)[42]

6.2.4.6 *Swelling Index*

The, previously weighed (w_1), tablets were placed individually in a petri-dish containing 10ml of distilled water. The weight of the tablet (w_2) after 30min was noted down after wiping the excess water from the tablet using a filter paper. The swelling index was calculated using the formula[44]:

$$\text{Swelling Index} = \frac{W_2 - W_1}{W1} X100$$

Equation 2

6.2.4.7 *Wash-off Test*

The mucoadhesive properties of the tablets were evaluated by wash-off method. Pieces of buccal mucosa of goat were mounted on the glass slides provided with suitable support. After fixing 2 tablets to this glass slide by pressing them onto the pre-wet tissue for 30sec, it was tied to the arm of tablet disintegration test apparatus (with the cylindrical drug chambers removed) and was run at 37°C in pH 6.8 buffer. Time taken for the detachment of both the tablets was noted down[20].

6.2.4.8 *In vitro drug release study*

The dissolution study was carried out in a dissolution apparatus. The dissolution medium consisted of 900ml of pH 6.8 phosphate buffer. The temperature was set at 37 ± 0.5°C with a rotation speed of 50 rpm. The Ketoprofen buccal tablet was allowed to sink to the bottom of the vessel. Samples of 10ml were withdrawn at 10 min interval, filtered and analyzed by UV at 260nm.

6.2.4.9 ***Ex vivo drug permeation study***

The drug release from the formulated tablet was assessed using a Franz diffusion cell. The donor and the receptor chambers were separated by goat buccal mucosa. The receptor chamber was filled with pH 6.8 phosphate buffer. The temperature was set at 37 ± 0.5°C. Drug release from the buccal tablets was studied for a period of 1 hour per tablet. Samples of 1ml receptor fluid were withdrawn at 15min time interval and diluted to 10ml with pH 6.8 buffer solution. They were then analyzed by spectrophotometric method at 260 nm[45].

6.2.4.10 ***Drug Release Kinetics***

The release of drugs from the tablet can be characterisedusing various kinetic models[46].

- Zero order equation

The zero order release kinetics can be obtained by plotting cumulative % drug released (vs) time (hours). It is ideal for the formulation to have release profile of zero order to achieve pharmacological prolonged action.

$$\mathbf{C = K_o t}$$

Equation 3

Where, K_o = Zero order constant in conc. / time

t = Time in hours

- First order equation

The graph was plotted as log % cumulative drug remaining (vs) time in hours.

$$\mathbf{Log\ C = log\ C_o - Kt/2.303}$$

Equation 4

Where,

C_o = Initial drug concentration

K = First order constant

t = Time in hours.

- Higuchi Kinetics

The graph was plotted with % cumulative drug released (vs) square root of time.

$$Q = Kt^{½}$$

Equation 5

Where,

K = Constant reflecting design variable system (Differential rate constant)

t = Time in hours.

The drug release rate is inversely proportional to the square root of time.

- Korsmeyer – Peppas equation

To evaluate the mechanism of drug release, it was further plotted in Peppas equation as log cumulative % of drug released (vs) log time.

$$M_t/M_\alpha = Kt^n$$

Equation 6

Where,

M_t/M_α= Fraction of drug released at time t

t = Release time

K = Kinetics constant (Incorporating structural and geometric characteristics of the formulation)

n = Diffusional exponent indicative of the mechanism of drug release.

Table 4.16: Release mechanisms based on n-value

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

The n value obtained is used to characterize different release mechanisms for cylindrical shaped matrices.

- Hixson and Crowell erosion equation

To evaluate the drug release with changes in the surface area and the diameter of particles, the data were plotted using the Hixson and Crowell erosion equation. The graph was plotted by cube root of % drug remaining Vs Time in hours.

$$Q_o^{1/3} - Q_t^{1/3} = K_{HC}t$$

Equation 7

Where,

Qt = Amount of drug released at time t

Q_o = Initial amount of drug

K_{HC} = Rate constant for Hixson Crowell equation

Table 4.17: Parameters of release kinetics

Release Mechanism	Y – Axis	X - Axis
Zero-order Kinetics	% Cum. drug release	Time in min
First order Kinetics	Log % cum. drug remaining	Time in min
Higuchi kinetics	% cum. drug release	Square root of time
Korsmeyer-Peppas Equation	Log cum.% of drug release	Log time
Hixson and Crowell Equation	Cube root of % drug remaining	Time in min

6.2.4.11 *Prediction and optimization*

The results obtained from the wash-off time and *ex vivo* permeation study were selected as the key parameters for optimizing the formulations. The two responses were evaluated in an optimization-software: Design Expert® 8.0.7.1 issued by Statease. The responses were transformed into logarithmic values and analyzed by stepwise regression, where in, terms are added to the final response equation in steps by evaluating their significance. The predicted responses are compared with the actual values and the optimized formulation is set as the one with both good wash-off time and *ex vivo* permeation.

RESULTS & DISCUSSIONS

7 Results and Discussions

7.1 Results

7.1.1 Pre-compressional Evaluations

- The DSC analysis of the drug and polymer gave thermal profile characteristic of the substances.

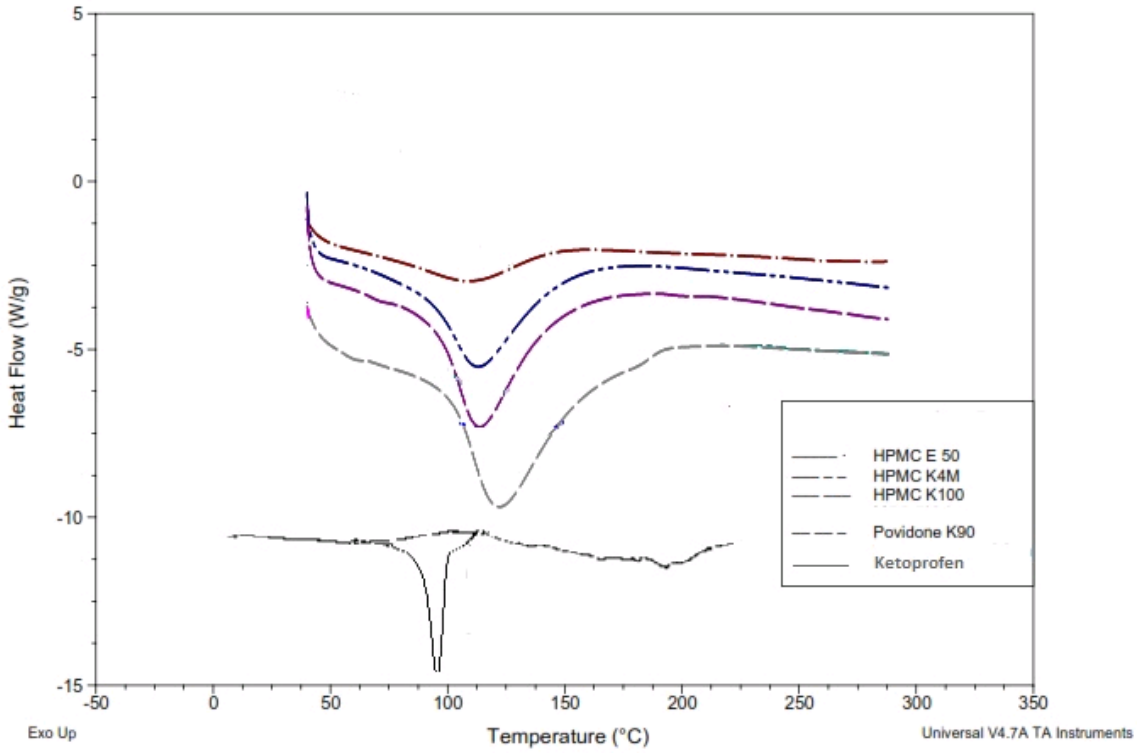


Figure 7.1: Overlay of DSC profiles of drug and polymers

- The assay of the drug, Ketoprofen showed that the drug was 99.7% pure.
- The particle size analysis of Ketoprofen is done by sieve method yielded the following results – 90.08µm (d_{ave})
- Solubility of Ketoprofen in pH 6.8 buffer at room temperature (28.5°C) was found to be 38.7 mg/ml[47]

7.1.2 Ketoprofen - Buccal Tablet Evaluations

7.1.1.1 *Uniformity of Weight:*

The results for the uniformity of weight are tabulated below.

Table 7.1: Uniformity of Weight

S.no.	Formulation Code	Uniformity of Weight (mg)*
1	DC.5.10.5	71.2 ± 2.16
2	DC.5.10.20	69.8 ± 1.95
3	DC.5.40.5	64.6 ± 1.26
4	DC.5.40.20	72.5 ± 3.86
5	DC.20.10.5	72.1 ± 1.69
6	DC.20.10.20	73.8 ± 1.66
7	DC.20.40.5	69.9 ± 3.52
8	DC.20.40.20	68.4 ± 1.91
9	WG.5.10.5	70.7 ± 3.82
10	WG.5.10.20	69.6 ± 1.45
11	WG.5.40.5	69.2 ± 1.94
12	WG.5.40.20	64.6 ± 1.26
13	WG.20.10.5	70.6 ± 1.95
14	WG.20.10.20	66.8 ± 1.23
15	WG.20.40.5	69.5 ± 2.23
16	WG.20.40.20	70.4 ± 3

Note: * Mean ± S.D.(n=20)

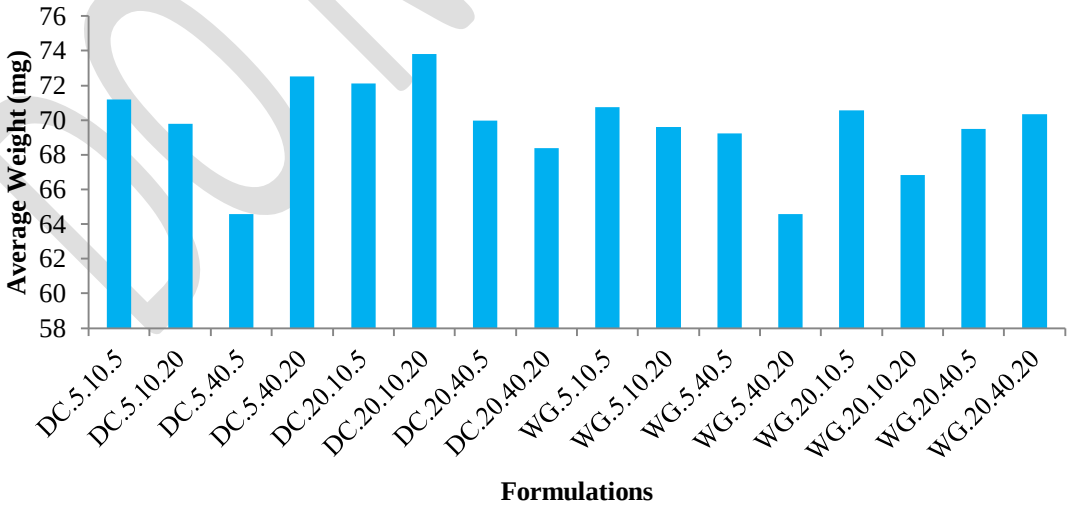


Figure 7.2: Uniformity of Weight

7.1.1.2 *Thickness of the Ketoprofen buccal tablet*

The results for the thickness of the Ketoprofen buccal tablets are tabulated below

Table 7.2: Average thickness of the Ketoprofen buccal tablets

S.no.	Formulation Code	Thickness (mm)*
1	DC.5.10.5	2.3 ± 0
2	DC.5.10.20	2.26 ± 0.055
3	DC.5.40.5	2.14 ± 0.055
4	DC.5.40.20	2.32 ± 0.045
5	DC.20.10.5	2.22 ± 0.045
6	DC.20.10.20	2.29 ± 0.055
7	DC.20.40.5	2.21 ± 0.022
8	DC.20.40.20	2.17 ± 0.067
9	WG.5.10.5	2.25 ± 0.05
10	WG.5.10.20	2.24 ± 0.055
11	WG.5.40.5	2.21 ± 0.022
12	WG.5.40.20	2.21 ± 0.022
13	WG.20.10.5	2.26 ± 0.055
14	WG.20.10.20	2.25 ± 0.05
15	WG.20.40.5	2.25 ± 0.05
16	WG.20.40.20	2.25 ± 0.05

Note:* Mean ± S.D. (n=10)

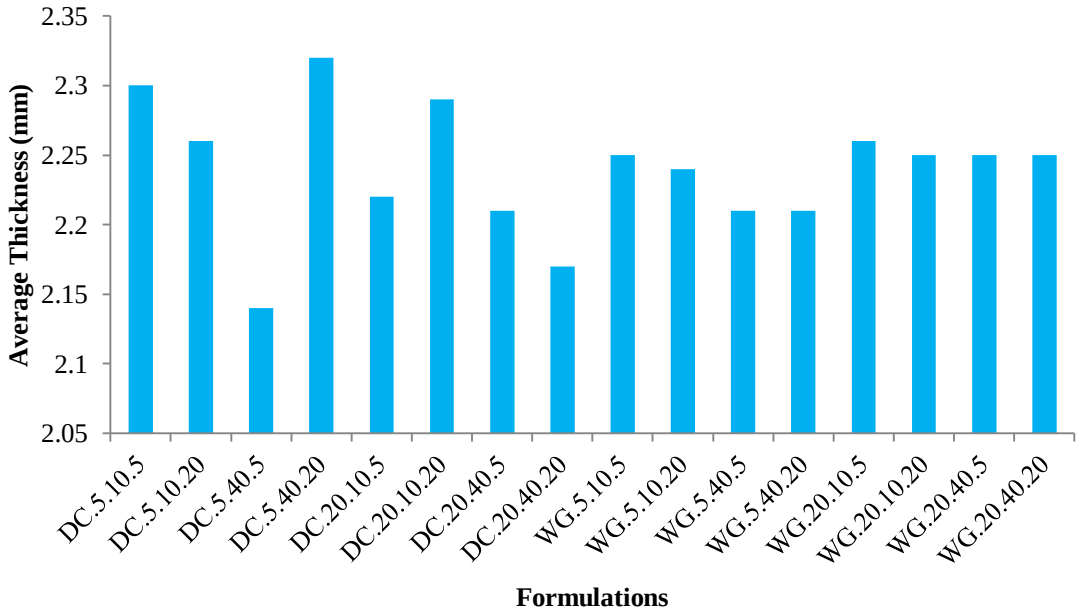


Figure 7.3: Average thickness of the Ketoprofen buccal tablets

7.1.1.3 *Hardness of the Ketoprofen buccal tablets:*

The results for the hardness of the Ketoprofen buccal tablets are tabulated below

Table 7.3: Average hardness of the Ketoprofen buccal tablets

S.no.	Formulation Code	Average Hardness (kP)*
1	DC.5.10.5	2.4 ± 0.06
2	DC.5.10.20	2.4 ± 0.06
3	DC.5.40.5	2.4 ± 0
4	DC.5.40.20	2.4 ± 0.06
5	DC.20.10.5	2.5 ± 0
6	DC.20.10.20	2.5 ± 0
7	DC.20.40.5	2.4 ± 0.06
8	DC.20.40.20	2.4 ± 0.06
9	WG.5.10.5	2.4 ± 0.06
10	WG.5.10.20	2.4 ± 0.06
11	WG.5.40.5	2.4 ± 0.06
12	WG.5.40.20	2.4 ± 0.06
13	WG.20.10.5	2.4 ± 0.06
14	WG.20.10.20	2.4 ± 0
15	WG.20.40.5	2.4 ± 0
16	WG.20.40.20	2.4 ± 0

Note 1:* Mean ± S.D. (n=3)

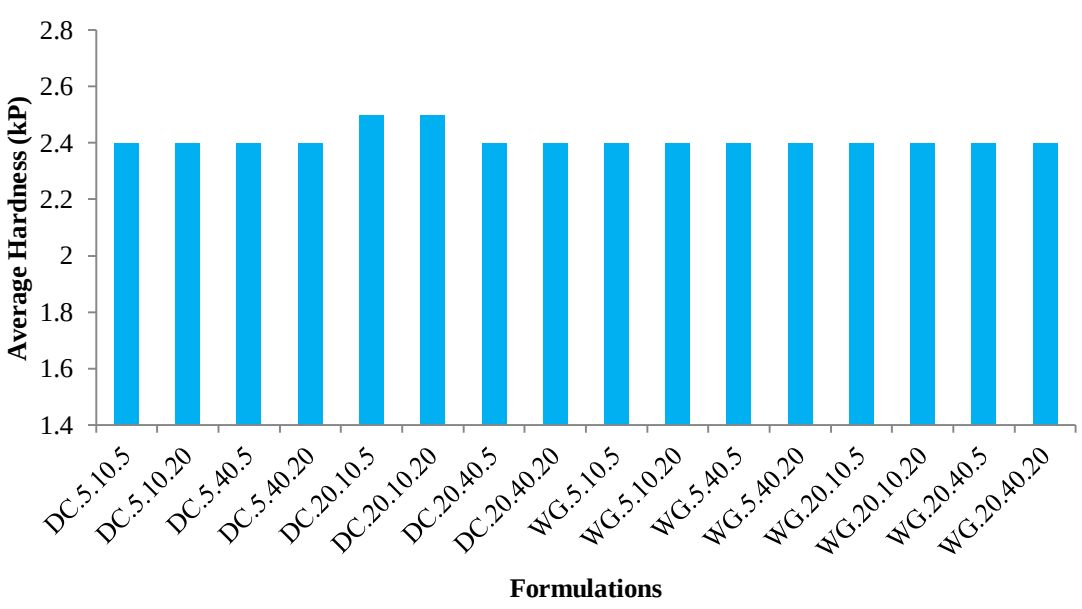


Figure 7.4: Average hardness of the Ketoprofen buccal tablets

7.1.1.4 *Friability of the Ketoprofen buccal tablets*

The results for the friability test for the Ketoprofen buccal tablets are tabulated below

Table 7.4: % Friability of the Ketoprofen buccal tablets

S.no.	Formulation Code	% Friability
1	DC.5.10.5	0.4740
2	DC.5.10.20	0.1164
3	DC.5.40.5	0.0000
4	DC.5.40.20	0.8700
5	DC.20.10.5	0.7760
6	DC.20.10.20	0.6009
7	DC.20.40.5	0.1270
8	DC.20.40.20	0.0007
9	WG.5.10.5	0.0004
10	WG.5.10.20	0.0025
11	WG.5.40.5	0.2704
12	WG.5.40.20	0.0013
13	WG.20.10.5	0.3830
14	WG.20.10.20	0.0673
15	WG.20.40.5	0.0025
16	WG.20.40.20	0.5554

The tablets are within the limits for friability.

7.1.1.5 *Drug content in the Ketoprofen buccal tablets*

The standard solution of Ketoprofen was prepared using pH 6.8 buffer. The serial dilutions were then analyzed by UV spectrophotometer at 260nm.

Table 7.5: Absorbance of standard solutions of Ketoprofen

Concentration µg/ml	Absorbance
0	0
15	0.092
30	0.203
45	0.298
60	0.394
75	0.512

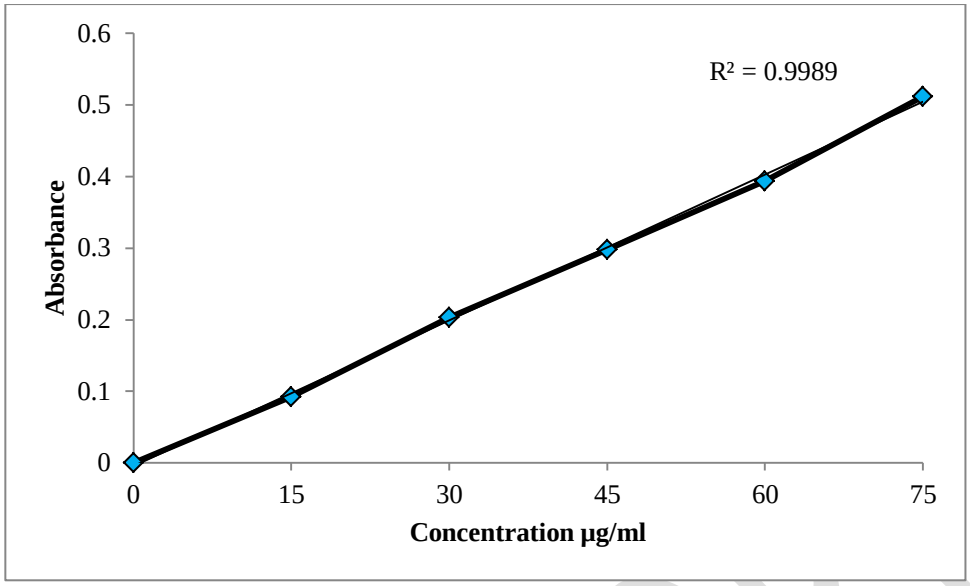


Figure 7.5: Standard plot for Ketoprofen @ pH 6.8

The Ketoprofen buccal tablets were designed to carry a drug load of 12.5mg/tablet.

Table 7.6: Assay values (%) and drug contents (mg) of the Ketoprofen buccal tablets

S.no.	Formulation Code	% Assay Values	Drug Content (mg)
1	DC.5.10.5	99.9	12.49
2	DC.5.10.20	99.7	12.46
3	DC.5.40.5	96.2	12.03
4	DC.5.40.20	100.9	12.61
5	DC.20.10.5	100.4	12.55
6	DC.20.10.20	101.8	12.73
7	DC.20.40.5	100.3	12.54
8	DC.20.40.20	98.3	12.29
9	WG.5.10.5	99.8	12.48
10	WG.5.10.20	99.2	12.40
11	WG.5.40.5	98.9	12.36
12	WG.5.40.20	99.1	12.39
13	WG.20.10.5	100.2	12.53
14	WG.20.10.20	97.1	12.14
15	WG.20.40.5	99.3	12.41
16	WG.20.40.20	100.5	12.56

The drug content in various formulations are found to be of satisfactory level.

7.1.1.6 *Swelling Index*

The swelling indices of the various buccal formulations are tabulated below

Table 7.7: Swelling index of the Ketoprofen buccal tablets

S.no.	Formulation Code	Swelling Index (%)
1	DC.5.10.5	0.62
2	DC.5.10.20	1.15
3	DC.5.40.5	2.22
4	DC.5.40.20	6.67
5	DC.20.10.5	3.57
6	DC.20.10.20	4.55
7	DC.20.40.5	1.92
8	DC.20.40.20	1.01
9	WG.5.10.5	1.11
10	WG.5.10.20	0.43
11	WG.5.40.5	1.00
12	WG.5.40.20	2.10
13	WG.20.10.5	0.25
14	WG.20.10.20	2.04
15	WG.20.40.5	1.00
16	WG.20.40.20	0.44

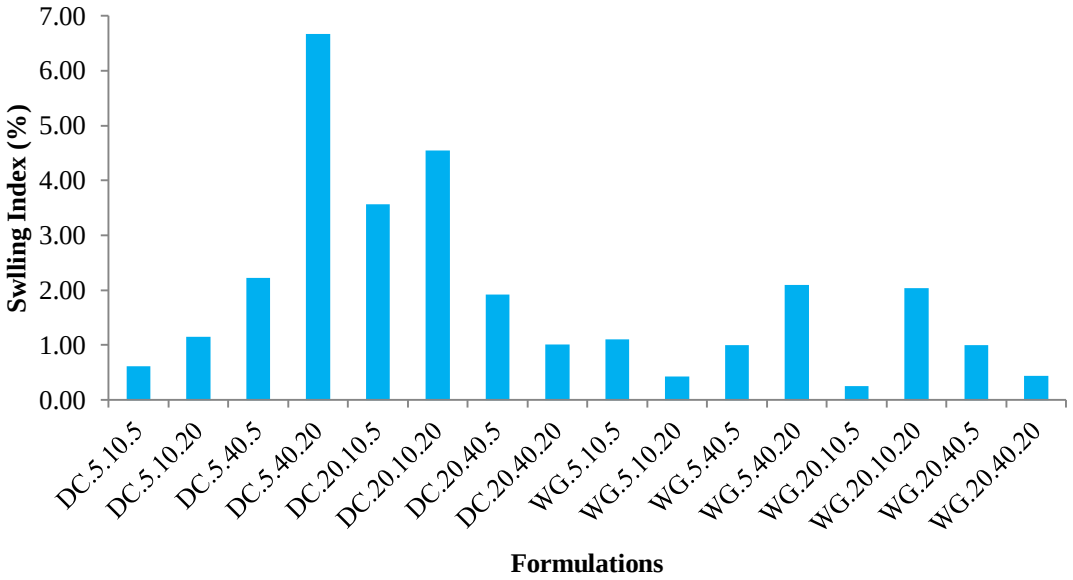


Figure 7.6: Swelling index of the Ketoprofen buccal tablets

7.1.1.7 *Wash-off test*

The data from the Wash off test are tabulated below.

Table 7.8: Time duration of attachment of the Ketoprofen buccal tablets

S.no.	Formulation Code	Attachment Time (min)
1	DC.5.10.5	15
2	DC.5.10.20	10
3	DC.5.40.5	12
4	DC.5.40.20	20
5	DC.20.10.5	23
6	DC.20.10.20	21
7	DC.20.40.5	24
8	DC.20.40.20	18
9	WG.5.10.5	6
10	WG.5.10.20	8
11	WG.5.40.5	5
12	WG.5.40.20	14
13	WG.20.10.5	10
14	WG.20.10.20	16
15	WG.20.40.5	11
16	WG.20.40.20	18

Note 2: 0-10 min > Poor adhesion strength; 10-30min > Low adhesion strength

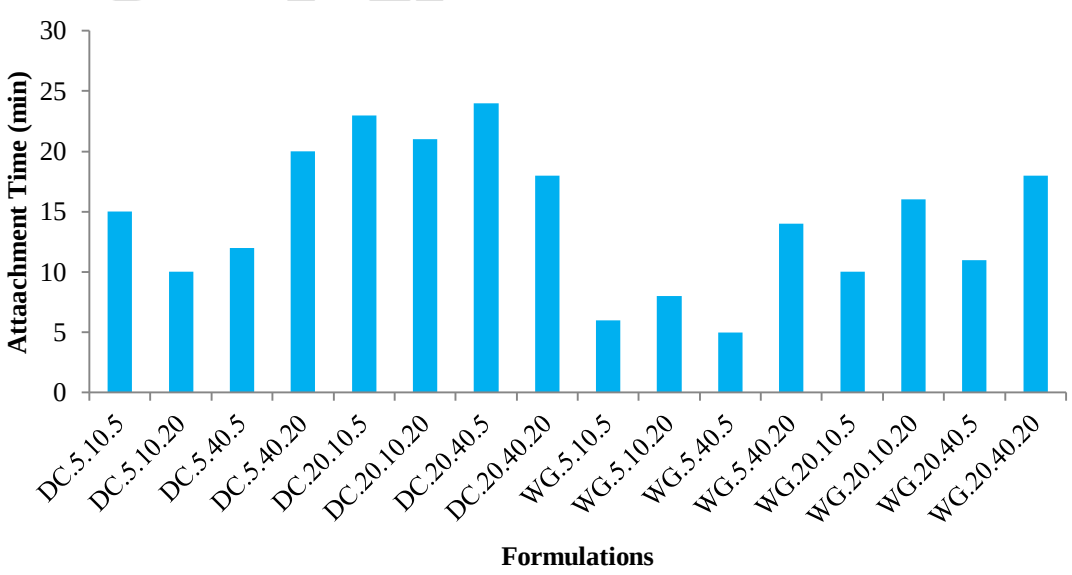


Figure 7.7:Time duration of attachment of the Ketoprofen buccal tablets

7.1.1.8 *In vitro drug release study*

Table 7.9: *In vitro* drug release profile of Ketoprofen buccal tablet formulations 1-4

Formulation Code	DC.5.10.5	DC.5.10.20	DC.5.40.5	DC.5.40.20
Time (min)	% Drug Released			
0	0	0	0	0
10	89.4	84.6	90.3	91.9
20	97.3	98.1	99.4	98.7
30	99.1	99.3	99.5	99.6
40	99.7	99.8	99.7	99.6
50	-	-	-	-
60	-	-	-	-

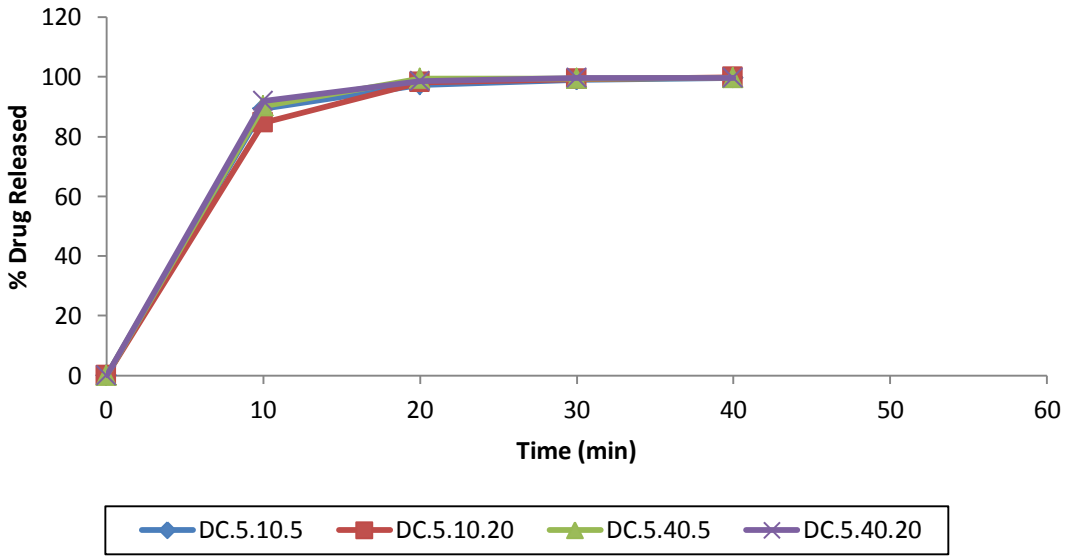


Figure 7.8: *In vitro* dissolution profiles of Ketoprofen buccal tablet formulations 1-4

Table 7.10: *In vitro* drug release profile of Ketoprofen buccal tablet formulations 5-8

Formulation Code	DC.20.10.5	DC.20.10.20	DC.20.40.5	DC.20.40.20
Time (min)	% Drug Released			
0	0	0	0	0
10	91.1	91.5	86.3	87.6
20	99.1	98.6	95.2	97.1
30	99.6	99.6	98.5	98.3
40	99.7	99.6	99.7	99.8
50	-	-	-	-
60	-	-	-	-

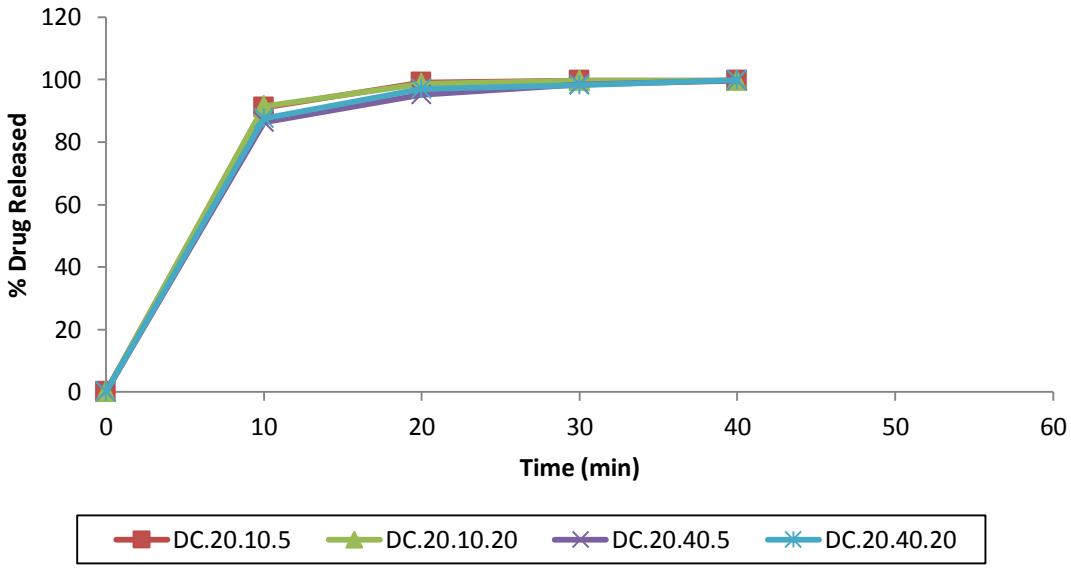


Figure 7.9: *In vitro* dissolution profiles of Ketoprofen buccal tablet formulations 5-8

Table 7.11: *In vitro* drug release profile of Ketoprofen buccal tablet formulations 9-12

Formulation Code	WG.5.10.5	WG.5.10.20	WG.5.40.5	WG.5.40.20
Time (min)	% Drug Released			
0	0	0	0	0
10	82.1	30.2	60.4	72.5
20	94.4	80.2	88.2	97.7
30	99.4	96.3	99.6	99.2
40	99.6	97.2	99.6	99.4
50	-	99.3	-	-
60	-	-	-	-

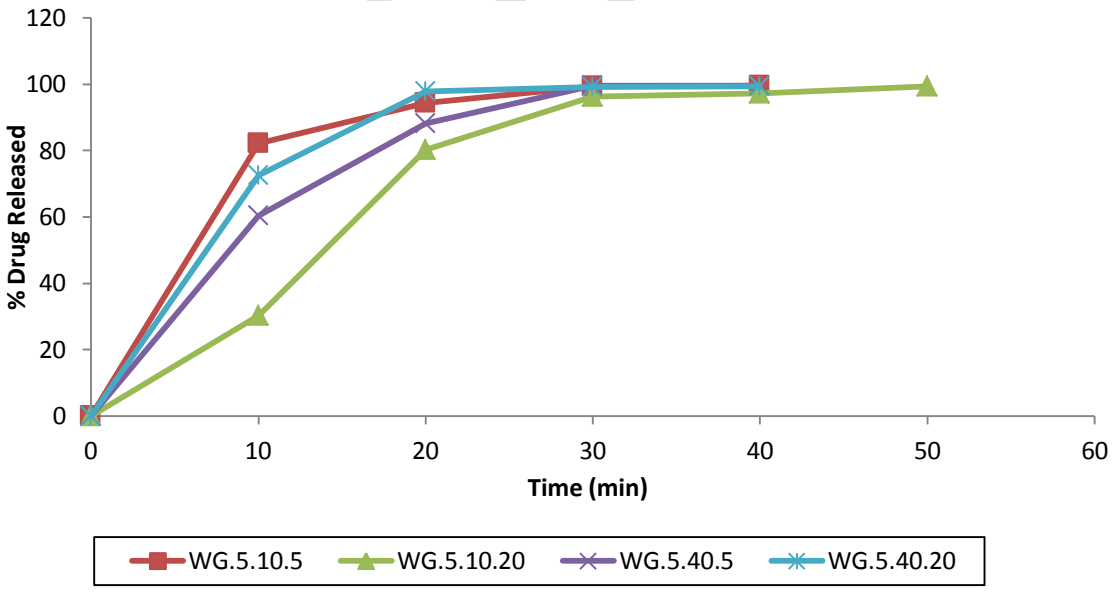


Figure 7.10:*In vitro* dissolution profiles of Ketoprofen buccal tablet formulations 9-12

Table 7.12:*In vitro* drug release profile of Ketoprofen buccal tablet formulations 13-16

Formulation Code	WG.20.10.5	WG.20.10.20	WG.20.40.5	WG.20.40.20
Time (min)	% Drug Released			
0	0	0	0	0
10	10.3	76.2	62.2	32.9
20	24.2	96.1	90.8	87.4
30	52.3	98.3	98.4	98.3
40	95.2	99.7	99.4	99.8
50	99.4	-	-	-
60	-	-	-	-

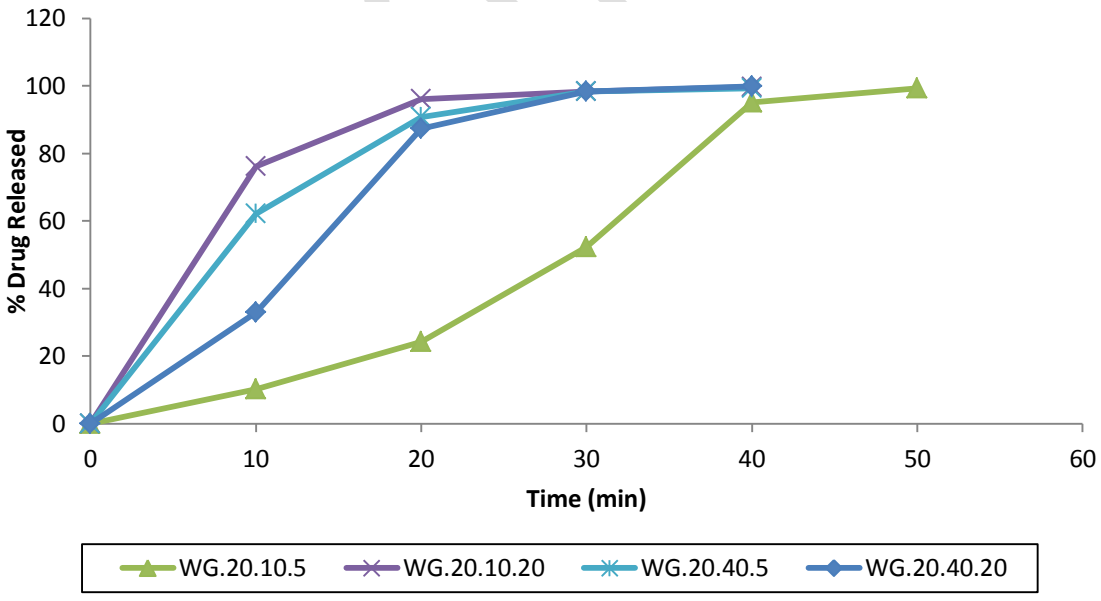


Figure 7.11: In vitro dissolution profiles of Ketoprofen buccal tablet formulations 13-16

7.1.1.9 *Ex vivo drug permeation study*

The drug permeation data for the various Ketoprofen buccal tablet formulations is given below.

Table 7.13: *Ex vivo* drug permeation data for Ketoprofen buccal tablet formulations 1-4

Formulations	DC.5.10.5	DC.5.10.20	DC.5.40.5	DC.5.40.20
Time (min)	Amount of drug permeated (%)			
0	0.000	0.000	0.000	0.000
15	12.982	6.553	3.493	2.874
30	26.608	13.257	10.012	10.180
45	33.930	21.021	16.532	12.212
60	39.635	28.604	23.039	17.065

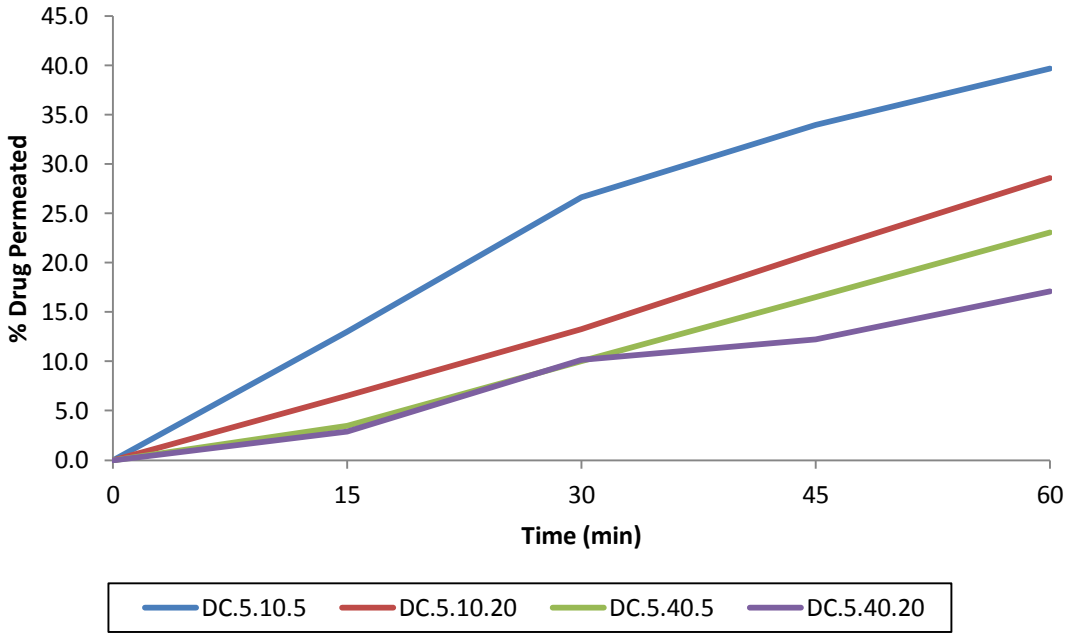


Figure 7.12: *Ex vivo* drug permeationfor Ketoprofen buccal tablet formulations 1-4

Table 7.14: *Ex vivo* drug permeation data forKetoprofen buccal tablet formulations 5-8

Formulations	DC.20.10.5	DC.20.10.20	DC.20.40.5	DC.20.40.20
Time (min)	Amount of drug permeated (%)			
0	0.000	0.000	0.000	0.000
15	3.033	10.256	8.547	13.130
30	5.330	15.926	13.105	16.882
45	9.499	29.478	17.930	27.021
60	10.746	32.113	19.316	32.676

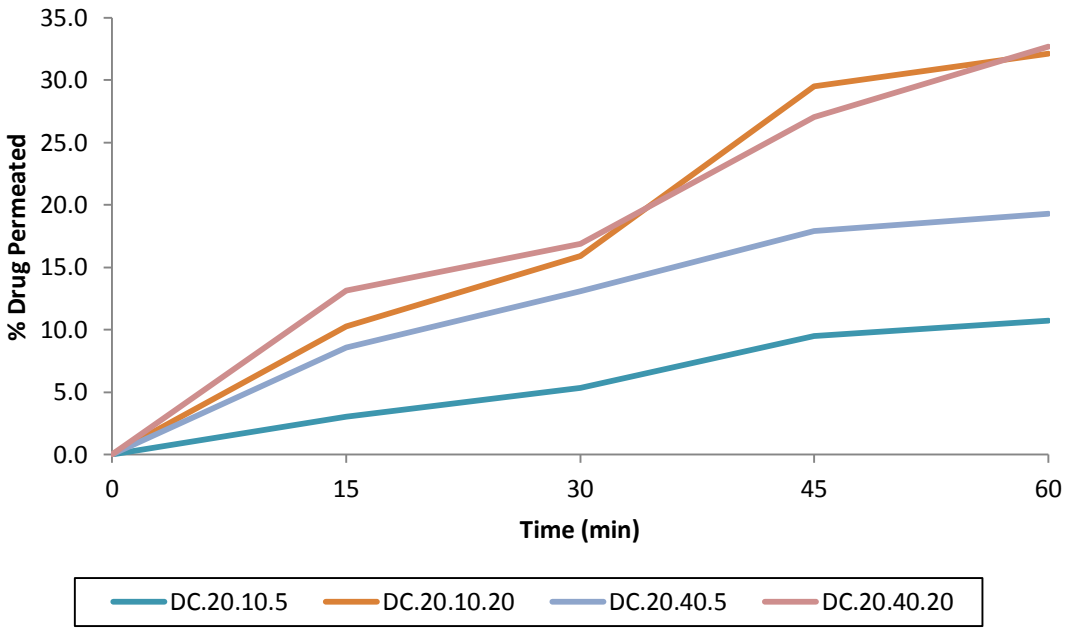


Figure 7.13: *Ex vivo* drug permeationfor Ketoprofen buccal tablet formulations 5-8

Table 7.15: *Ex vivo* drug permeation data for Ketoprofen buccal tablet formulations 9-12

Formulations	WG.5.10.5	WG.5.10.20	WG.5.40.5	WG.5.40.20
Time (min)	Amount of drug permeated (%)			
0	0.000	0.000	0.000	0.000
15	5.516	3.508	1.852	1.581
30	8.787	6.885	5.394	3.096
45	12.614	8.571	8.167	4.577
60	17.748	11.583	10.318	7.640

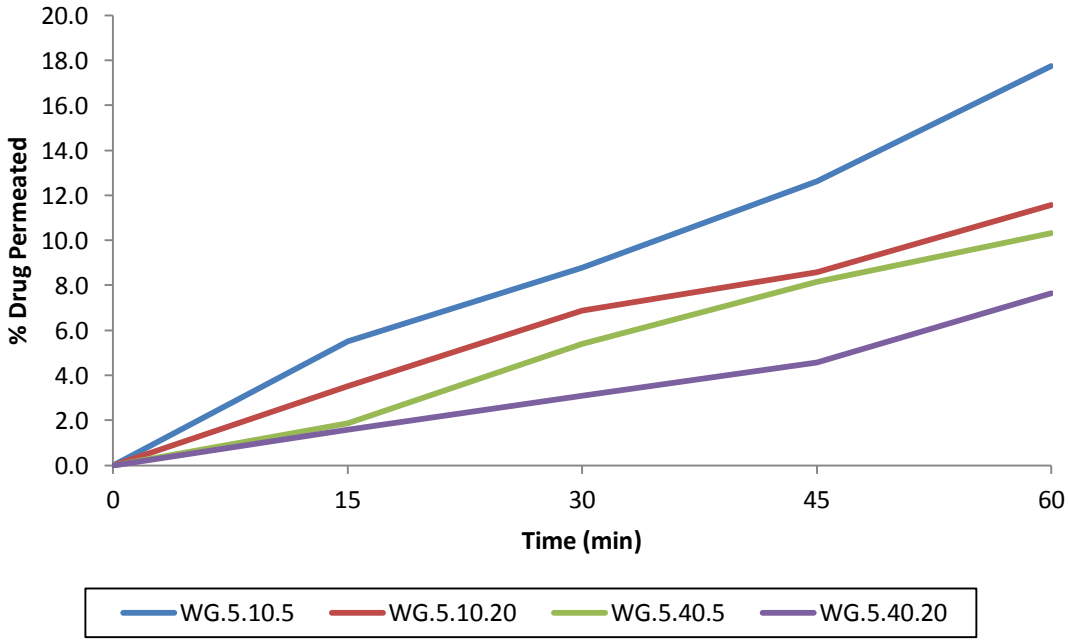


Figure 7.14: *Ex vivo* drug permeation for Ketoprofen buccal tablet formulations 9-12

Table 7.16: *Ex vivo* drug permeation data for Ketoprofen buccal tablet formulations 13-16

Formulations	WG.20.10.5	WG.20.10.20	WG.20.40.5	WG.20.40.20
Time (min)	Amount of drug permeated (%)			
0	0.000	0.000	0.000	0.000
15	0.217	1.941	0.783	0.503
30	0.955	2.220	2.331	0.968
45	3.406	2.220	5.475	1.461
60	4.351	2.230	7.821	2.271

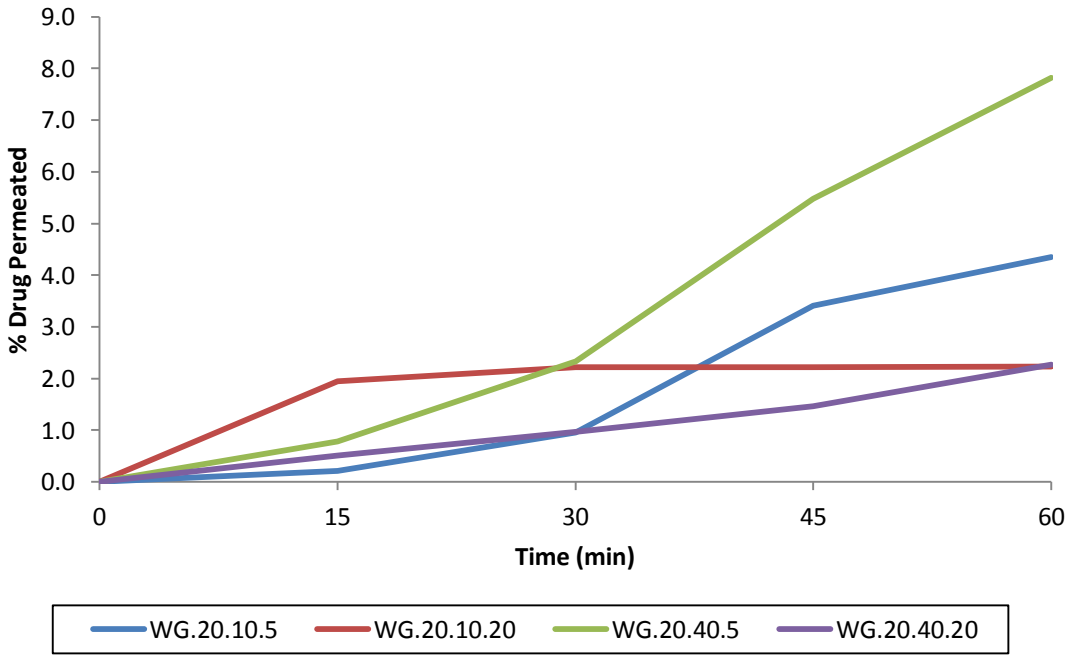


Figure 7.15: *Ex vivo* drug permeation for Ketoprofen buccal tablet formulations 13-16

7.1.1.10 *Drug release kinetics for the buccal tablet formulations*

Table 7.17: Ketoprofen release kinetics and mechanisms from Ketoprofen buccal tablet formulations

Formulation	R^2					n	Release Order	Release Mechanism
	Zero Order	First Order	Higuchi	Hixon Cromwell	Peppas			
DC.20.10.20	0.9696	0.9699	0.9696	0.9698	0.936	0.175	First order	Erosion
DC.20.10.5	0.9816	0.9817	0.9816	0.9464	0.941	0.19	First order	Erosion
DC.20.40.20	0.9725	0.9751	0.9725	0.9743	0.975	0.139	First order	Diffusion
DC.20.40.5	0.9387	0.9417	0.9387	0.9407	0.923	0.12	First order	Erosion
DC.5.10.20	0.9985	0.9976	0.9985	0.9979	0.968	0.212	Zero order	Erosion
DC.5.10.5	0.9677	0.972	0.9677	0.9706	0.882	0.156	First order	Erosion
DC.5.40.20	0.9747	0.975	0.9747	0.9749	0.839	0.24	First order	Erosion
DC.5.40.5	0.9897	0.9884	0.9897	0.9889	0.933	0.268	Zero order	Erosion
WG.20.10.20	0.951	0.9508	0.951	0.9509	0.933	0.378	Zero order	Erosion
WG.20.10.5	0.9096	0.9093	0.9096	0.9094	0.927	0.446	Zero order	Fickian Diffusion
WG.20.40.20	0.9861	0.9859	0.9861	0.986	0.988	0.214	Zero order	Erosion
WG.20.40.5	0.9542	0.9535	0.9542	0.9537	0.956	0.337	Zero order	Diffusion
WG.5.10.20	0.9873	0.988	0.9873	0.9877	0.936	0.165	First order	Erosion
WG.5.10.5	0.9928	0.9928	0.9928	0.9928	0.994	0.168	Zero order	Diffusion
WG.5.40.20	0.9732	0.9723	0.9732	0.9726	0.989	0.222	Zero order	Diffusion
WG.5.40.5	0.9913	0.9914	0.9913	0.9914	0.893	0.242	First order	Erosion

Note 3: For *ex vivo* permeation study

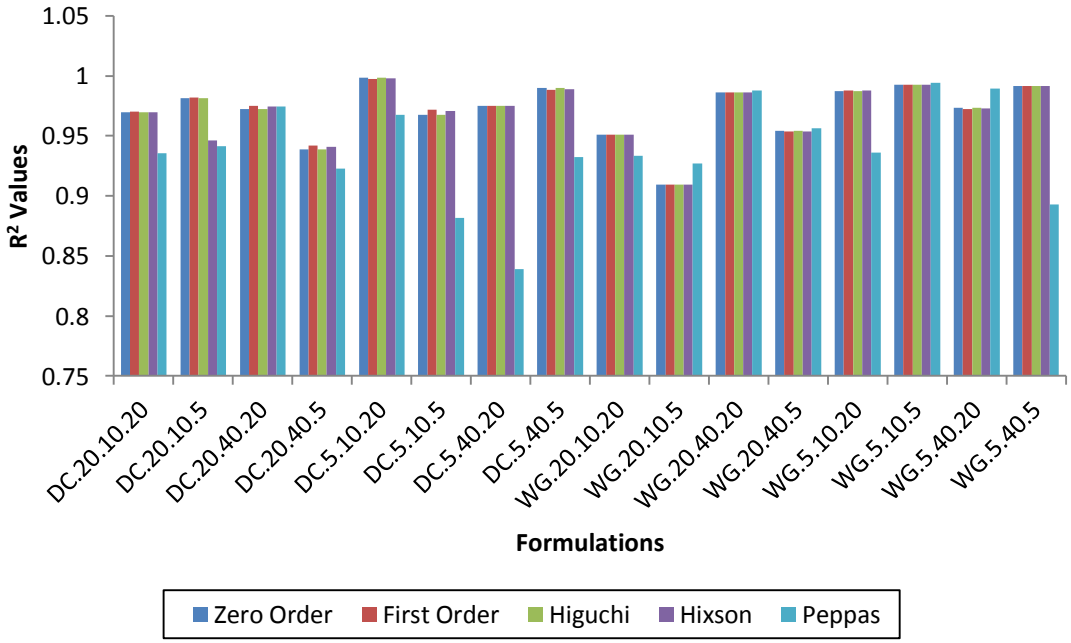


Figure 7.16: R^2 values of release kinetics and mechanisms

7.1.1.11 *Prediction and Optimization*

Final Equation in Terms of Actual Factors:
(Wash off Time)

Method of preparation		Direct Compression
Log10(Wash off Time)		=
	1.257960255	
	0.00561609	* HPMCK4M
	-0.009720428	* HPMCK100
	-0.024291635	* HPMCE50
	0.000556938	* HPMCK4M * HPMCK100
	0.001068979	* HPMCK4M * HPMCE50
	0.001094929	* HPMCK100 * HPMCE50
	-5.89503E-05	* HPMCK4M * HPMCK100 * HPMCE50

Method of preparation		Wet Granulation
Log10(Wash off Time)		=
	0.795886981	
	0.00561609	* HPMCK4M
	-0.009720428	* HPMCK100
	-0.005811862	* HPMCE50
	0.000556938	* HPMCK4M * HPMCK100
	0.001068979	* HPMCK4M * HPMCE50
	0.001094929	* HPMCK100 * HPMCE50
	-5.89503E-05	* HPMCK4M * HPMCK100 * HPMCE50

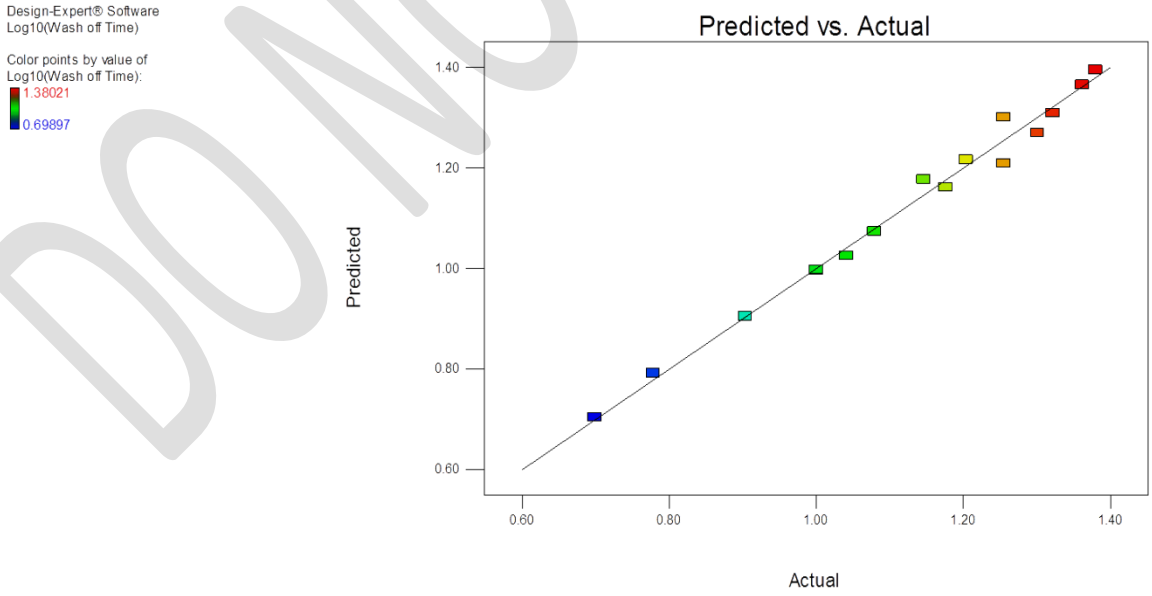


Figure 7.17: Plot of predicted value (vs) actual value for wash-off time

Final Equation in Terms of Actual Factors:
(***Ex vivo* Permeation**)

Method of preparation		Direct Compression
Log10(Ex vivo permeation in 1h)		=
	2.054637985	
	-0.064706819	* HPMC K4M
	-0.014704174	* HPMC K100
	-0.026930738	* HPMC E50
	0.001296803	* HPMC K4M * HPMC K100
	0.00320541	* HPMC K4M * HPMC E50
	0.000280888	* HPMC K100 * HPMC E50
	-4.14834E-05	* HPMC K4M * HPMC K100 * HPMC E50

Method of preparation		Wet Granulation
Log10(Ex vivo permeation in 1h)		=
	1.645025056	
	-0.051099913	* HPMC K4M
	-0.014704174	* HPMC K100
	-0.011867337	* HPMC E50
	0.001296803	* HPMC K4M * HPMC K100
	-9.95567E-05	* HPMC K4M * HPMC E50
	0.000280888	* HPMC K100 * HPMC E50
	-4.14834E-05	* HPMC K4M * HPMC K100 * HPMC E50

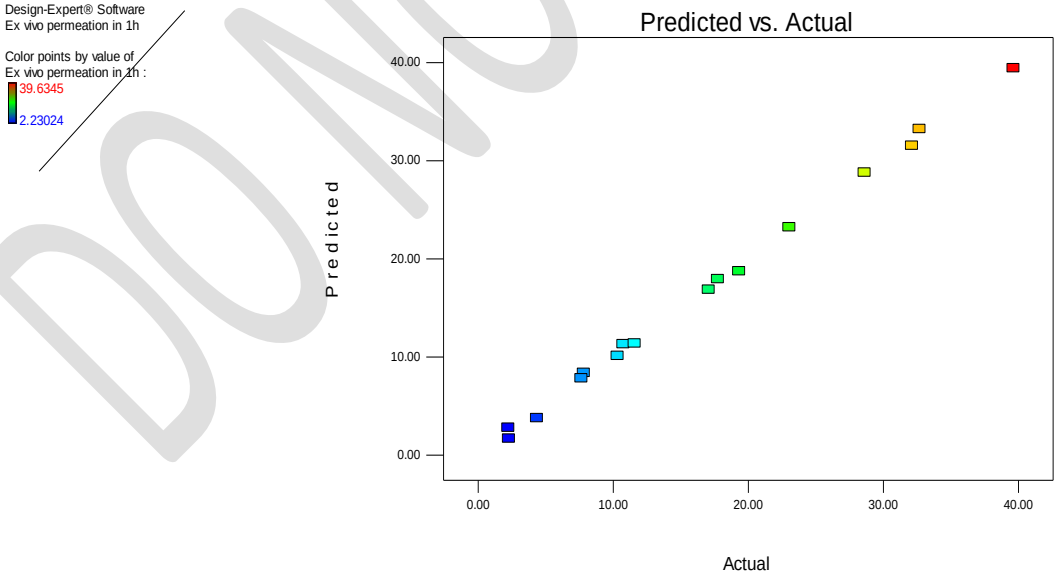


Figure 7.18: Plot of predicted value (vs) actual value for *Ex vivo* permeation

The formulations were optimized for the highest wash-off time and *ex vivo* permeation values.

The optimized formulation was found to be: DC.20.10.20

Table 7.18: Parameters of optimized formulation

Method of Preparation	(%) HPMC K4M	(%) HPMC K100	(%) HPMC E50	Actual Wash off Time (min)	Actual *ex vivo permeation (%)*	Predicted Wash off Time (min)	Predicted *ex vivo* permeation (%)
Direct Compression	20	10	20	21	32.1132	20.3896	32.1081

The formulation DC.20.10.20 follows diffusion cum erosion type of release.

7.2 Discussions

7.2.1 Pre-compressional and Formulation parameters

- The excipients and the drug Ketoprofen have no interactions[47].
- They showed their characteristic DSC profiles, Ketoprofen-melting point ≈95°C; HPMC- transition temperature ≈ 100 – 200°C; and povidone, softening point ≈ 150°C , ensuring their identity.
- The drug assay proved that the Ketoprofen supplied was of pharmacopoeial standards.
- The solubility profile of the drug revealed, it is highly soluble in pH 6.8 buffer [47].
- The particle size determination of the drug, Ketoprofen confirmed that it can be used in a direct compression.

7.2.2 Uniformity of weight

Although the Ketoprofen buccal tablets are within the permissible limits for weight deviation, **(Table 7.1)** the extreme variations could have been avoided by careful monitoring of the tablet weights during the punching process (in process quality control).

7.2.3 Thickness of the Ketoprofen buccal tablets

The average thickness **(Table 7.2)** of the Ketoprofen buccal tablets was found to be quite uniform with minimum variation. The thickness of the tablet and hence its total weight must be reduced in order to obtain good mucoadhesion, as the mucoadhesive property is also dependent on the geometry of the dosage form.

7.2.4 Hardness and friability of the Ketoprofen buccal tablets:

The hardness of the Ketoprofen buccal tablets (**Table 7.3)**are low, but the friability data **(Table 7.4)** suggests that the tablets are quite robust enough to withstand the normal handling.

7.2.5 Drug content analyses

All the buccal tablet formulations have quite satisfactory drug content **(Table 7.6)** the content could have been more uniform just as in the case of the tablet weights, since it depended upon the experience and skill level of the tablet punching machine operator.

7.2.6 Swelling Index

Swelling index is an important parameter in judging the mucoadhesion property, at least in the initial stages, since water uptake is important for the polymers to uncoil and interact with the mucin. The swelling indices of the Ketoprofen buccal tablets **(Table 7.7)** reveals that while the buccal tablet formulations are all made of hydrophilic materials, the extent of swelling differs based on the individual tablet composition. The swelling indices of the first three formulations are quite low because of the fact that they started to disintegrate and lose mass soon after placing them upon the petri-dish. The formulations containing higher levels of the polymers HPMC K100 and HPMC E50 displayed the highest swelling index. The reason for this is because, they are of lower viscosity grade and hence the water penetration in to the tablet matrix is facilitated by them[19]. The tablets prepared by dry granulation showed greater swelling compared to the ones made by wet granulation. This could be attributed to the increased cohesion between the granules in case of the formulations prepared by wet granulation technique. But this is counter intuitive since, the wet granulation technique incorporated PVP K90 which is hydrophilic polymer and also it contains lesser quantity of Magnesium stearate, which is the key hydrophobic excipient in the formulation.

7.2.7 Wash-off time

All the formulations displayed low-poor mucoadhesion (**Table 7.8**). This may be attributed to the effect of the filler/diluent material. The presence of MCC in the formulation enhanced both the disintegration of the tablet matrix and the deprivation of the water molecules for the mucoadhesive polymers. It has been previously discussed that a high diluent level reduces the mucoadhesion property of the formulations [48]. The poor attachment time can also be attributed to the low concentration of polymer in the formulations[27]. Barring the effect of the diluent, the other factors that affect the attachment time arethe method of preparation. As seen with the previous effect, swelling index, direct compression leads to slightly better attachment time. Similarly, the presence of high concentration of HPMC K4M aslo contributes to the higher mucoadhesion time while the other two grades, K100 and E50 gave a relatively smaller negative effect. The dual interactions between the three polymers had a positive effect on the wash-off time. The triple interaction of the polymer inflicted a very slight negative effect. (as evidenced from the response equation.)

7.2.8 *In vitro* drug release

All the formulations had good release, >99% within 50min (**Table 7.9-7.12)**. This can be attributed to the fact that all the excipients used except the glidant – Magnesium stearate, are hydrophilic in nature. The polymers, at their maximum level, are only 60% of the drug content. This and the fact that the drug, Ketoprofen has high solubility in pH 6.8, contribute to the relatively fast dissolution rate.

7.2.9 *Ex vivo* drug permeation

The release profiles of the various buccal tablet formulations **(Table 7.13-7.16)** reveal that the drug release from the direct compression tablets is at a greater rate than from the wet granulation batches. The higher levels of polymers, especially HPMC K4M retarded the release from the buccal tablet. This is evident from the equation for the *ex vivo* permeation, the coefficient for HPMC K4M is the largest – signifying that it is the major contributor while the coefficients of K100 and E50 are relatively smaller. The dual interactions between the polymers, however, were conducive of drug permeation and therefore, drug release. The three way interaction between the polymers gave a relatively smaller negative contribution to the response, *ex vivo* permeation.

7.2.10 Drug release kinetics

The drug release kinetics is predominantly first order for the Ketoprofen buccal tablets manufactured by direct compression method and predominantly zero for those manufactured by wet granulation method **(Table 7.17)**. The release mechanism was found to be Fickian diffusion coupled with erosion of the tablet matrix. The diffusion is attributed to the presence of HPMC polymer (high viscosity – K4M) and the erosion is primarily due to the rapidly hydrating MCC and low viscosity HPMC polymers, K100 and E50.

7.2.11 Prediction and optimization

The predicted values of response were in agreement with the actual values. Hence this model can be adapted to study the effects of the different formulation parameters. Furthermore, the model can be used to predict globalized responses after apt experimentation.

SUMMARY

8 Summary

In the present work, effect of different formulation and process variables, method of preparation – direct compression or wet granulation, different levels of HPMC K4M, HPMC K100 and HPMC E50, on the buccal tablets of Ketoprofen were studied. The buccal tablet formulations were determined by the 2-full factorial experimental design – $2^{n,}$ where, n is the number of independent variables. Ketoprofen buccal tablets can be of great help to geriatric patients on anti-hypertensive treatment who suffer from tooth ache.

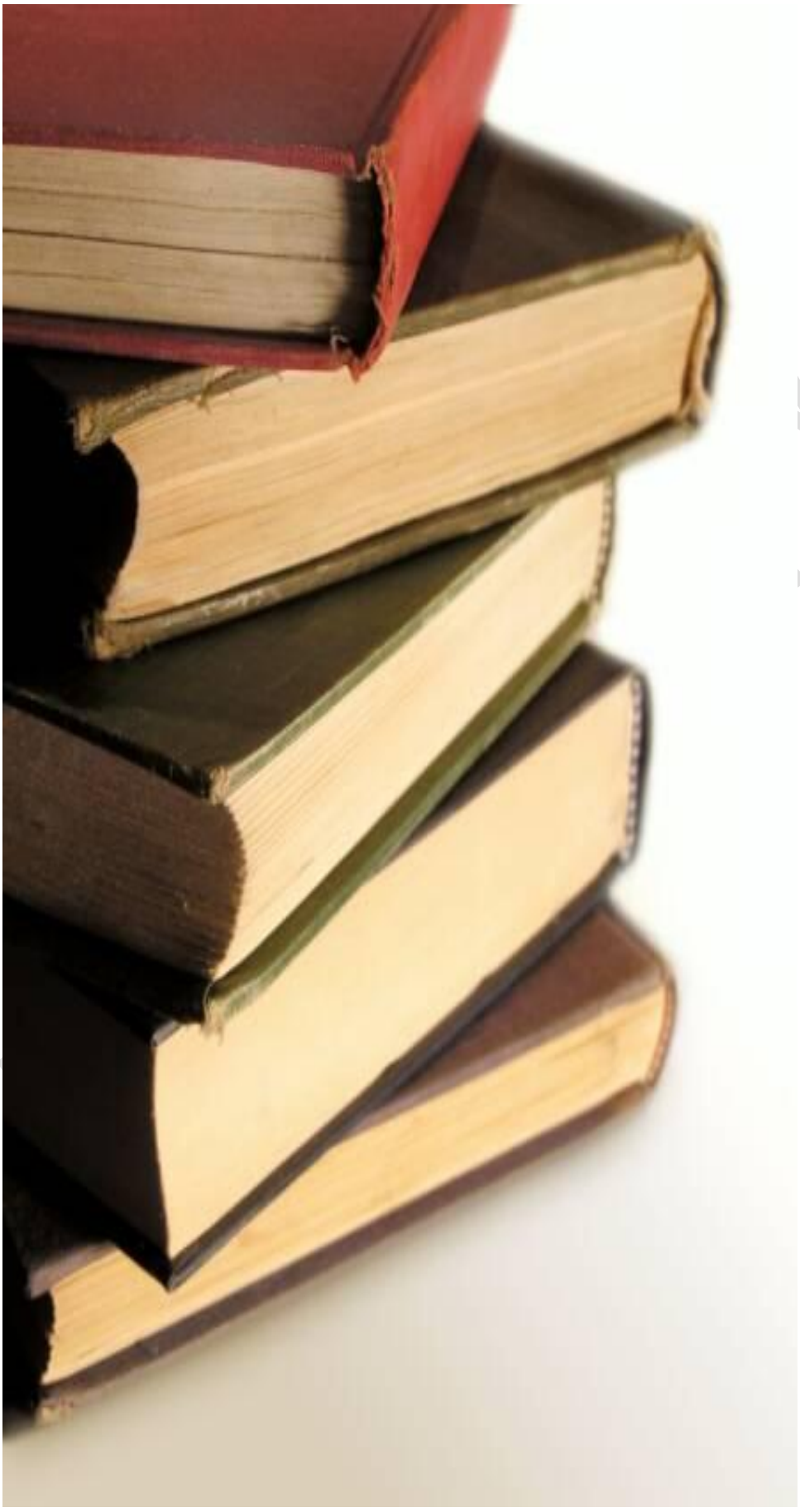
- The different grades of the polymer HPMC – (K4M, K100, E50) were used as the buccal-adhesive polymers.
- The buccal tablets were tested for weight uniformity, thickness, friability and hardness.
- They were then evaluated for their swelling index, *in vitro* drug release, wash-off time – indirect measure of adhesion strength, and *ex vivo* drug permeation.
- The kinetics and mechanism of the drug permeation through the excised buccal tissue of goat from the buccal tablets were also characterized.
- The data collected were then analyzed using software to determine the effects of each parameter.
- The effects of the various parameters involved were then interpreted.

CONCLUSION

9 Conclusion

Ketoprofen buccal tablets were manufactured by both direct compression method and wet granulation method using different levels and combinations of the polymers HPMC K4M, K100 and E50. Solubility of Ketoprofen was determined - 38.7 mg/ml in pH 6.8 buffer by equilibrium solubility method. 2^4 full Factorial design showed that the direct compression method was suitable for the preparation of Ketoprofen buccal tablets. The prepared buccal tablets' physical characteristics were evaluated and they complied with the official pharmacopoeial limits. The *in vitro* dissolution results revealed that the drug release was more than 95% within 45min, suggesting high solubility of Ketoprofen in pH 6.8 buffer. The Wash-off time of the tablets gave an indirect measure of their mucoadhesive property. The step-wise regression equation indicates that the polymers interact in multiple ways. But the method of preparation and the presence of low viscosity polymers had the greatest effect on this property. The *ex vivo* permeation study indicated the drug was highly permeable (≈40% within 1 hour). The polymer interaction contributed positively in two-way interactions and was negative in case of three-way interactions. The contribution of the individual polymers had shown negative effect. Therefore the formulation - DC.20.10.20, had the optimum response values among all the formulations. Hence, it can be considered for further study.

Given the ease of manufacture of the dosage form and the extensive data available on the drug candidate, the formulation can be considered for marketing in the near future after suitable studies.



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