



Research Article

FORMULATION DEVELOPMENT AND CHARACTERIZATION OF MUCOADHESIVE PATCH OF ATENOLOL

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ABSTRACT

The buccal region of oral cavity is an attractive site for administration of drug of choice. Buccal route is an excellent for systemic delivery of drug providing great bioavailability. A significant reduction in dose and dosing frequency can be achieved, thereby reducing dose dependent side effects, patient compliance and prolonging duration of action. Buccal dosage form increase bioavailability and prevent first pass metabolism of drug. The present study involves formulation and evaluation of patch of atenolol using chitosan with a hydrophilic polymer like PVP K-30 in various proportions and combinations fabricated by solvent casting technique. Propylene glycol has been used as plasticizer as well as penetration enhancer. Atenolol an antihypertensive drug which undergoes first pass metabolism with $t_{1/2}$ 6-7 hrs. Various physicochemical parameters like weight variation, thickness, folding endurance, drug content, water vapour transmission moisture content, moisture absorption, in vitro and ex vivo drug release, in-vitro permeation, stability in simulated saliva and various mucoadhesion parameters like mucoadhesive strength, force of adhesion and bond strength were evaluated. The swelling percentage was found to be function of solubility of drug and PVP K-30. The mucoadhesive strength, vapour transmission and *in-vitro* release of water-soluble drug through water insoluble chitosan base matrix were found satisfactorily. All the fabricated patches were able to sustain for 6 hrs and the optimized formulation obeyed Korsmeyer-Peppas release kinetics. The physical appearance of patch was examined by scanning electron microscopy.

Keywords: Patch, Bioadhesion, Mucoadhesive Buccal Delivery.

INTRODUCTION

Conventional routes of drug administration such as oral, intramuscular and intravenous have, in many cases, been supplanted by the advent of new, novel drug delivery systems. The systemic delivery of drugs through novel methods of administration is one area in which significant changes and improvements have been made. Consequently, precise control of drug input into the body by a variety of routes is now possible. Controlled and sustained release formulations have been developed and are gaining in popularity and medical acceptance. Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over injectables and oral delivery. Buccal delivery of drugs provides an attractive alternate to other conventional methods of systemic drug

administration since buccal mucosa is relatively permeable with rich blood supply and acts as an excellent site for the absorption of drugs. Research had been focused on placing a drug delivery system in a particular region of the body for maximizing biological drug availability and minimizing dose-dependent side effects. The administration of drugs via buccal route facilitates a direct entry of drug molecules into the systemic circulation, avoiding the first pass metabolism and drug degradation in the harsh gastrointestinal environment, which are often associated with oral administration. The buccal cavity is easily accessible for self-medication, and hence it is safe and well accepted by patients, since patch can be very easily applied and even removed from the application site, terminating the, input of

drug whenever desired. Moreover, patch provide more flexibility than other drug delivery system. Chitosan has been used in a wide variety of biomedical applications like sustained release of drugs. Being a non-toxic, biocompatible and biodegradable polymer, chitosan has been widely used for pharmaceutical and medical applications. A wide variety of pharmaceutical applications for chitosan have been reported over the last two decades due to its preservative and haemostatic properties. It has also been used as a pharmaceutical excipient in conventional dosage forms as well as in novel applications involving bioadhesion and transmucosal drug transport.

Atenolol is a β_1 selective adrenergic receptor antagonist and a class IV antihypertensive agent prescribed widely in diverse cardiovascular diseases. e.g. hypertension, angina pectoris, arrhythmias and myocardial infarction. The oral absorption of drug from oral dosage forms is about 90% but it is subjected to a very extensive first-pass metabolism in the liver and its bioavailability is only about 40%. Atenolol have poor membrane permeability in the gastrointestinal tract due to its hydrophilic nature, as it is sparingly soluble in water and having low partition coefficient. This drug has a short half-life of 6-7 hours. The short half-life and extensive first pass metabolism of atenolol makes it a suitable candidate for administration via a buccal delivery system that provides sustained drug delivery without pre-systemic metabolism. For the sustained action of atenolol through oral mucosal route, 50 mg drug had been incorporated. Atenolol is selected as model drug because of its short half-life (6-8hrs.), low molecular weight and low dose (25-50 mg), which makes it a suitable candidate for administration by buccal route. The mucoadhesive, natural and unique polymer, chitosan was the base of dosage form.

MATERIALS AND METHODS:

Materials: Atenolol was obtained as gift sample from Ranbaxy Laboratories Ltd, New Delhi, India; Chitosan was provided by Central Institute of Fisheries Technology, Cochin as gift sample; Polyvinyl Pyrrolidone K-30 was obtained from Loba labs, New Delhi, India. The other chemicals used were of analytical grade.

Preparation of Atenolol mucoadhesive patch

Drug-Excipient Interaction Studies:

a) Physical compatibility: The Drug excipients study was performed with the help of glass vials and accurately weighed mixture of drug and polymer combinations were placed into them separately. Four sets of prepared physical mixture were placed in glass vials which were then tightly sealed. Vials were kept at 25^o C and 40^o C for 4 weeks, after which the vials were opened and observed for caking, liquefaction, discoloration and odour or gas formation.

b) Chemical compatibility (FT-IR analysis of drug – excipients): There is always a possibility of drug-excipients interaction in any formulation due to their intimate contact. The technique employed in this study to know drug-excipients interactions is IR spectroscopy; IR spectroscopy is one of the most powerful analytical techniques which offer the possibility of chemical identification. Infra-red spectra of pure drug atenolol and formulations were scanned by using Perkin-Elmer FTIR 1600, by a thin film method.

PROCEDURE

The buccal mucoadhesive patches from chitosan polymer were prepared by solvent casting technique in different concentration. Table -1 contains the composition of prepared patch. For preparation of backing layer, a glass petri dish of 9 cm diameter was used as a casting surface. Backing membrane of ethyl cellulose was fabricated by slowly pouring a solution containing 1g of ethyl cellulose and 2% dibutyl phthalate in 20 ml ethanol to the glass petri dish and air drying in hot air oven for 1 hr. The polymeric solution of chitosan was prepared using 1.5% (V/V) acetic acid in distilled water under occasional stirring for 48 h. The resulting viscous chitosan solution was filtered through nylon gauze to remove debris and suspended particles. The drug release characteristic was increased by use of a water-soluble hydrophilic additive polyvinylpyrrolidone (PVP K-30) into the chitosan solution under constant stirring. Propylene glycol (5%, V/V) was added as plasticizer as well as penetration enhancer under constant stirring. The resultant solution was left overnight at room temperature to ensure a clear, bubble-free solution. The solution was poured onto backing membrane glass petri dish having 9 cm. diameter. The amount of drug required to dissolve in petri dish, so patch of 2 cm diameter size containing 50 mg of atenolol was calculated by the ratio of surface area of petri dish and

patch (1cm²). The dummy patch without drug was also prepared. The Petri dishes were kept on levelled surface and covered by inverted funnel to allow controlled evaporation of solvent at room temperature till a flexible film was formed. Dried films were carefully removed, checked for any imperfections or air bubbles and cut into patches of 2 cm in diameter by using fabricated punch. The patch containing 50 mg of atenolol drug was packed in aluminum foil and stored in an airtight glass container to maintain the integrity and elasticity of the patches.

inspection of patches and evaluation of texture by feel or touch.

Thickness and weight uniformity

The thickness of three randomly selected patch from every batch was determined using a standard screw gauge. Weight uniformity of patch was determined by taking weight of ten patches of sizes 2cm diameter from every batch and weigh individually on electronic balance.

Surface PH study

The surface pH of patch was determined in order to -

Table 1: Composition of Atenolol buccal mucoadhesive patches

| Formulation Code | Chitosan ^a (20 ml) | PVP K -30 (mg) | Propylene Glycol | Drug ^b (mg/63.58.cm ² area) |
|------------------|-------------------------------|----------------|------------------|--|
| Placebo | 1.0% | 50 | 5% | ----- |
| F ₁ | 1.0% | 50 | 5% | 1000 |
| F ₂ | 1.0% | 100 | 5% | 1000 |
| F ₃ | 1.0% | 150 | 5% | 1000 |
| F ₄ | 1.5% | 50 | 5% | 1000 |
| F ₅ | 1.5% | 100 | 5% | 1000 |
| F ₆ | 1.5% | 150 | 5% | 1000 |
| F ₇ | 2.0% | 50 | 5% | 1000 |
| F ₈ | 2.0% | 100 | 5% | 1000 |
| F ₉ | 2.0% | 150 | 5% | 1000 |

^a Chitosan solution has been made in 1.5 % acetic acid.

^b 50 mg drug per 1x1 cm ² patch.



Fig-1: Blank polymeric buccal patch

Evaluation of patch

Physical Appearance and Surface Texture: Include visual

investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined glass electrode was used for this purpose. The patch was allowed to swell by keeping it in contact with 1 ml of distilled water for 1 hour at room temperature. The pH was measured by bringing the electrode in contact with the surface of the patch and allowing it to equilibrate for 1 minute. The experiments were performed in triplicate, and average values were reported.

Drug Content uniformity

The drug contents in the patch were determined by dissolving 2 cm diameter patch in 25 ml phosphate buffer saline (pH=7.4) and shaken vigorously for 24 hrs at room temperature. These solutions were filtered through

Whatman® filter paper (No. 42). After proper dilution, optical density was measured spectrophotometrically using a UV-VIS spectrophotometer (UV-1700 Double beam spectrophotometer, SHIMADZU Corporation, Japan) at 274 nm. The experiments were carried out in triplicate.

Folding endurance

Folding endurance of the patch was determined by repeatedly folding one patch at the same place till it broke or folded upto 300 times manually, which was considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of folding endurance. This test was done on randomly selected three patches from each.

Swelling percentage study

Swelling study of prepared patch was calculated by function of weight and area increase due to swelling, which was measured for each formulation as follows.

Patch was weighed (W), placed in a 2% w/v agar gel plate and incubated at 37±1°C. At regular 1 hr. Time intervals (up to 3 h.), the patch was removed from petri plate and excess surface water was removed carefully by blotting with a tissue paper. The swollen patch was then reweighed (W₁) and the swelling index was calculated from the formula

$$\% \text{ Swelling Index} = (W_1 - W) / W \times 100$$

The experiment was carried out in triplicate and their average values were determined.

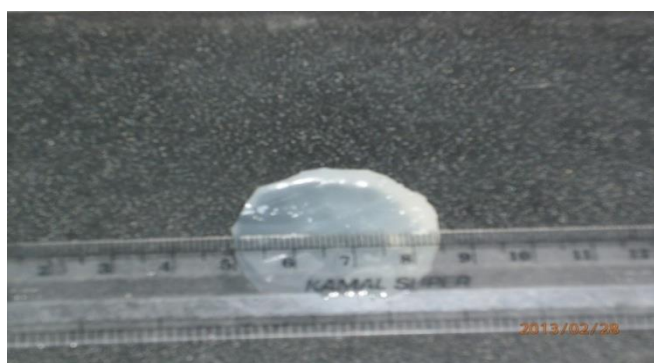


Fig -2 Increase in diameter due to swelling of buccal patch

Water Vapour transmission test (WVTR)

Water Vapour transmission method was employed for the determination of water vapour transmission from the patch. Glass-bottle (length= 5 cm, narrow mouth with internal

diameter =0.8 cm) filled with 2 g anhydrous calcium chloride and an adhesive (Feviquick®) spread across its rim, was used in the study. The patch was fixed over the adhesive and the assembly was placed in a constant humidity chamber, prepared using saturated solution of ammonium chloride and maintained at 37±2°C. The difference in weight for 1 week was calculated daily. The experiments were carried out in triplicate and water vapour transmission rate was obtained as follows:

$$\text{VTR} = (\text{Amount of moisture transmitted}) / (\text{Area} \times \text{Time})$$

In vitro residence time

In vitro residence time was determined employing a modified USP disintegration apparatus. The disintegration medium was composed of 900 ml isotonic phosphate buffer of pH 7.4 phosphate buffer maintained at 37±0.5°C. A piece of cellophane membrane of 4cm length was used for this study. The membrane was attached to a rectangular glass piece using cyanoacrylate adhesive from non-mucosal surface. The mucoadhesive patch was hydrated from one surface using pH 7.4 phosphate buffer and then the hydrated surface was brought into contact with cellophane membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the patch was completely immersed in buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the film (patch) from cellophane membrane surface was observed and recorded (n=3).

Percentage moisture absorption (PMA)

This test was carried out to check the physical stability of the buccal films at high humid conditions. In the present study, the moisture absorption capacity of the films was determined as follows. Three 2cm diameter films were cut out and weighed accurately then the films were placed in a desiccator containing saturated solution of aluminum chloride, keeping 75% relative humidity inside the desiccators. After 3 days, the films were removed, weighed and percentage moisture absorption was calculated.

$$\text{Percentage moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Percentage moisture content (PMC)

The patch was weighed accurately and kept in desiccators containing anhydrous calcium chloride. After 3 days, the patches were taken out and weighed. The moisture content (%) was determined by calculating moisture loss (%) using the formula:

$$\text{Moisture content (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

This test is of great significance as variation in moisture content causes a significant variation in mechanical properties of film especially when film comprises of hygroscopic components, it is also important to assess such polymers, which are of humidity-dependent diffusiveness. The capacity of film to take up water is an important intrinsic parameter of the polymeric system in consideration to the release of drug through mucous membrane.

Bioadhesive Strength

The tensile strength required to detach the polymeric patch from the mucosal surface was applied as measure of the bioadhesive performance. The fabricated balance above was used for the bioadhesion studies. The semipermeable membrane was fixed to the movable platform. The mucoadhesive patch of 2cm diameter was fixed to the stainless steel lamina using 'fevi-quick' as adhesive. The exposed patch surface was moistened with 1 ml of isotonic phosphate buffer for 30 seconds for initial hydration and swelling. The platform was then raised upward until the hydrated patch was brought into contact with mucosal surface. A preload of 20 gms was placed over the stainless steel lamina for 3 minutes as initial pressure. And then weights were slowly increased on the right pan, till the patch detaches from the mucosal membrane. The weight required to detach the patch from the mucosa give the bioadhesive strength of the mucoadhesive patch. The procedure is repeated for 3 times for each patch and mean value of the 3-trials was taken for each set of formulation. After each measurement the tissue was gently and thoroughly washed with isotonic phosphate buffer and left for 5 minutes. The following parameters were calculated from the bioadhesive strength:

$$\text{Force of adhesion (N)} = (\text{Bioadhesive strength (g)} \times 9.81) / 1000$$

$$\text{Bond strength (N m}^{-2}\text{)} = \text{Force of adhesion} / \text{Disk surface area}$$



Fig-3: Fabricated bioadhesion testing instrument

In vitro Release Study:

The USP dissolution apparatus 2 (paddle) was used to study the drug release from patch. The dissolution medium consisted of 250 ml of pH 7.4 PB. The release was performed at $37 \pm 0.5^\circ\text{C}$, at a rotation speed of 50rpm. One side of the patch was attached to a glass disk with instant adhesive (cyanoacrylate). The disk was put in the bottom of the dissolution vessel so that the patch remained on the upper side of the disk. Samples (5ml) were withdrawn by using calibrated pipette at pre-determined time (30 mins.) intervals and replaced with fresh medium. The samples were assayed spectrophotometrically at 274 nm.

In vitro permeation study

The in vitro buccal permeation study of atenolol buccal film (patch) through the cellophane membrane was performed using Franz diffusion cell at $37^\circ\text{C} \pm 0.2^\circ\text{C}$. Freshly boiled cellophane membrane was mounted between the donor and receptor compartments. The film (patch) was placed on the mucosa so the smooth surface of the mucosa placed towards receptor compartment and the compartments were clamped together. The donor compartment was filled with 1ml of phosphate buffer (pH 6.8). The receptor compartment was filled with isotonic phosphate buffer (pH 7.4) stirred with a magnetic bead at 50 rpm.

2 ml sample was withdrawn at predetermined intervals and replaced with fresh buffer solution and assayed by UV spectrophotometer at 274nm.

Stability in simulated human saliva:

The stability of the patches was studied in simulated saliva solution (pH 6.8) which was prepared by dissolving Na_2HPO_4 (2.38g), KH_2PO_4 (0.19g), NaCl (8.0g), per liter of distilled water adjusted with phosphoric acid pH 6.8. Patches were placed in separate petridishes containing 5ml of simulated saliva and kept in a temperature controlled oven at $37 \pm 0.2^\circ\text{C}$ for 6 h. At regular intervals (0, 2, 4 and 6 h), the patches were examined for physical changes like color, texture and shape.

Ex-vivo permeability study:

The test was carried out on optimised patch using fresh goat buccal mucosa which was obtained from a local slaughter house because of non-keratinized buccal mucosa similar to that of human. The modified Franz diffusion cell (3.14 cm²) was used to permeation studies, it consists of two compartments, one is donor compartment and another is receptor compartment of 25 ml capacity. The donor compartment contains 1 ml of pH 6.8 phosphate buffer. The receptor compartment is covered with water jacket to maintain temperature 37°C . The separated buccal epithelium was mounted between the two chamber, and in receptor chamber phosphate buffer solution having pH 7.4 was filled and buccal epithelium was allowed to stabilize for a period of 1 hr. after stabilization, patch was kept on epithelium and periodically (for 6 h) samples were withdrawn and maintained sink condition. The aliquots were analyzed spectrophotometrically at 274 nm. The drug permeation was correlated with cumulative drug released.

Drug release kinetic study

To describe the kinetics of the drug release from the matrix base the data obtained was fitted to different equations and kinetic models and percent drug release and release kinetics of atenolol from optimized formulation was determined. The kinetic mathematical models such as zero-order, first order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas models were used. The criterion for selecting the most appropriate model was chosen on the basis of the goodness-of fit test.

Stability Studies

The assessment procedure for the stability of a pharmaceutical product lies in the capability of a particular formulation in a specific container/ closure system to remain

within its physical, chemical, microbiological, therapeutic and toxicological specification stability studies pursue particular aims.

- a) Selection of the optimal formulation during pharmaceutical-technological development.
- b) Derivation of periods of stability, which ensure that the product retains its full activity up to the end of its shelf-life.

The atenolol patch were stored at room temperature ($27^\circ\text{C} \pm 1$), at 52% relative humidity and at 75% relative humidity and the drug content was determined spectrophotometrically.

Scanning electron microscopy

Film morphology was characterized by scanning electron microscopy. Samples were mounted on round brass stubs (12mm diameter) using double-backed adhesive tape and then sputter coated for 8 min at 1.1 kV under argon atmosphere with gold palladium before examination under the scanning electron microscope (JEOL JSM-6100 Scanning Electron Microscope, Japan). The images were captured on an Ilford PANF 50 black and white 35mm film.

RESULTS AND DISCUSSION

RESULTS

Physical Appearance and Surface Texture:

The patches were found to be smooth in texture on touching and appeared colorless to light yellow.

Thickness and weight

The thickness and weight variation might be due to increasing concentration of chitosan and PVP K-30. Thickness and weights of formulations were determined by standard deviation for ten determinations. Table-2 shows the thickness and weight of the formulated patches.

Surface pH

The surface pH of all formulations was nearer to neutral (≈ 7) and hence no mucosal irritation was expected. Table-2 shows the surface pH of the formulated patches.

Drug content uniformity

The drug content in the patch ranged from 90.69 ± 1.1 to $98.91 \pm 0.4\%$, indicating the favourable drug loading and patches uniformity with respect to drug content. Drug content uniformity of ten formulations were determined. Table-2 shows the drug content uniformity of formulated patches.

Swelling percentage study: The increasing order of swelling

percentage of batches was found to be $F9 > F8 > F6 > F7 > F3 > F5 > F2 > F4 > F1 > \text{Placebo}$. Due to poor aqueous solubility of chitosan, the placebo chitosan base matrix shown less swelling index. The results clearly mentioned that increasing concentration of PVP K-30 as well as chitosan increases the swelling percentage. PVP K-30 increased the surface wettability and consequently water penetration within the matrix. Table 3 shows various characteristics of patches.

Water Vapour transmission test (WVTR)

The formulation batches F1, F4 and F7 of chitosan formulation indicate less vapour transmission as compared to other chitosan based patch on day seven. The highest vapour permeation $1.95 \times 10^{-3} \pm 0.26 \times 10^{-3} \text{ g cm}^{-2} \text{ h}^{-1}$ was found with patch F3 on day seven. While less permeation $0.63 \times 10^{-3} \pm 0.11 \times 10^{-3} \text{ g cm}^{-2} \text{ h}^{-1}$ was found on day seven with patch F7, containing higher concentration of water insoluble chitosan and less PVP K-30. Water Vapour transmission through patches gives the idea of good permeability, but after that patch became saturated and no more moisture absorbed or transmitted. Table -5: shows water vapour transmission rate through the patches at different time intervals

Percentage moisture absorption and Percentage moisture loss:

By checking the physical stability of the film at high humid conditions and integrity of the film at dry conditions, the films were evaluated for PMA and PML and results were found to be in same order $\text{Placebo} > F3 > F2 > F1 > F6 > F5 > F4 > F9 > F8 > F7 > F6$.

The moisture uptake content was found to increase with increasing concentration of PVP-K30 which is hydrophilic in nature. But decreased as the insoluble chitosan concentration was increased. Placebo showed the highest PML and PMA due to high conc. of PVP K -30 and low conc. of insoluble chitosan and also absence of drug. The low moisture content in the formulation is highly appreciable to protect from microbial contaminations and bulkiness of the patches. Again, low moisture content in formulations helps them to remain stable from being a completely dried and brittle film. Table 3 shows various characteristics of patches.

Bioadhesive Strength

The mechanical strengths required for detachment of patch from cellophane membrane are shown in table 3.

Mucoadhesion strength of batch F1 from 1% chitosan, F4 from 1.5% chitosan and F7 from 2% chitosan was found to be $4.48 \pm 0.10 \text{ g}$, $4.75 \pm 0.32 \text{ g}$ and $5.35 \pm 0.21 \text{ g}$ respectively. The patches had shown good bioadhesion properties. The bioadhesive strength of patch was stronger in absence of drug, while increasing the concentration of chitosan base with increasing PVP K-30 concentration has less but acceptable bioadhesive strength. Table 4: Bioadhesive parameters of atenolol patch

Folding endurance

Folding endurance did not vary when the comparison was made between plain films and drug loaded patches. Films did not show any cracks even after folding for more than 300 for all batches. Table-2 shows folding endurance of the formulated patches

In vitro residence time

Time required for the complete erosion or detachment of patch from the mucosa was found satisfactory. Table 5.14 shows order of decreasing the residence time $F3 < F6 < F2 < F9 < F1 < F5 < F4 < F8 < F7$. The increasing concentrations of PVP-K30 allow swelling the buccal patch and made hydrogen bonding weaker. The patch F7 has highest 4.13 ± 0.37 hour and batch F3 has less 2.51 ± 0.5 hour residence time. From the obtained data, we conclude that the Chitosan base has good bioadhesion properties in appropriate concentration, and good bond strength forming capacity with mucin. But as the concentration of PVP K-30 increases, the bioadhesion was found very less, may be due to hydrophilic natures which loosen the bond strength with mucosal area. So patch might be detached as it absorbed water molecule. Table 3 shows various characteristics of patches.

In vitro release study: The drug release increased linearly with increasing concentration of PVP K-30 from batches F1 to F3, F4 to F6, and F7 to F9 containing 1%, 1.5 %, and 2 % Chitosan base respectively. The maximum in vitro release was found to be 98.6 % over a period of 6 hr. in formulation F6, containing 20 ml of 1.5 % chitosan base and highest concentration of PVP K-30. The drug release finding showed that the increase in water-soluble polymer PVP K-30 content results in faster swelling and release from patches.

Stability in simulated human saliva: All patches were subjected to investigation for stability in human saliva for 6 hrs. Patches

became shrank and small in size due to release of drug in saliva.

In vitro permeation Study:

All formulations were subjected to in vitro permeation study through cellophane membrane and showed max. release of 69 % drug permeation in 6 hrs.

Ex-vivo permeability study:

Optimized formulation (F6) was subjected to investigation of in ex-vivo permeability of drug and showed max. release 62.3 % drug permeation in 6 hr. from batch F6 through goat buccal mucosa.

Drug release kinetic study:

Data of the in vitro release were fit to different equations and kinetic models to explain the release kinetics of atenolol from these patch. The kinetic models used were a zero-order equation, first-order equation, Higuchi release and Korsmeyer & Peppas models. The best fit with the highest correlation coefficient (r) was shown by the korsmeyer & peppas model ($r^2 = 0.9911$, $n = 0.9878$) due to swelling nature of chitosan and which is a characteristic for swelling polymeric devices.

Accelerated stability studies:

Optimized formulation among all atenolol patches was subjected to 4 weeks storage at $45 \pm 0.5^\circ\text{C}$ & 75 ± 0.5 RH

and found that they retained their color as well as their elasticity. The percent atenolol released versus time demonstrates a decrease in the amount of drug released with time. Patches stored for 4 weeks released 89.1% drug in the same period. The decrease in release during storage may be a direct consequence of the reduced erosion rate of the patches.

Scanning electron microscopy:

The SEM photograph fig-15 (a),(b),(c) shows optimised formulation under different magnification which indicates the uniform dispersion of polymeric solution with drug molecule and patches shown porous surface, which may be suitable for the matrix system and shows uniformity of drug and polymers.

Conclusion:

A new buccoadhesive patches for controlled release of atenolol was developed using chitosan and PVP K-30 in various ratios. Chitosan has not only film forming but also has good bioadhesion properties. The drug release rate increases on inclusion of PVP K-30 into the chitosan base matrix system. It is concluded that chitosan with PVP K-30 can meet the ideal requirement for buccal patch which can bypass the extensive hepatic first pass metabolism and increase bioavailability of drug atenolol.

Table 2: Physicochemical characteristics of prepared patch of atenolol

| Formulation Code | Thickness ^a | Weight ^b Uniformity | Surface pH | Content uniformity | Folding endurance |
|------------------|------------------------|--------------------------------|-------------|--------------------|-------------------|
| Placebo | 0.47±0.001 | 36.53 | 5.89±0.081 | ----- | >300 |
| F ₁ | 0.64±0.04 | 56.61 | 5.67 ± 0.17 | 90.69±1.1 | > 300 |
| F ₂ | 0.71±0.02 | 59.81 | 5.47 ± 0.54 | 95.87 ±0.5 | > 300 |
| F ₃ | 0.75±0.07 | 61.42 | 5.42±0.093 | 97.16 ±0.2 | > 300 |
| F ₄ | 0.82±0.05 | 65.31 | 5.32±0.074 | 93.88 ±1.4 | > 300 |
| F ₅ | 0.99±0.01 | 69.38 | 5.09±0.042 | 97.82 ±0.7 | > 300 |
| F ₆ | 1.05±0.03 | 72.28 | 5.54±0.035 | 98.91 ±0.4 | > 300 |
| F ₇ | 1.11±0.02 | 71.75 | 5.76±0.056 | 82.93±1.09 | > 300 |
| F ₈ | 1.17±0.18 | 77.47 | 6.01±0.073 | 88.68±1.11 | > 300 |
| F ₉ | 1.22±0.81 | 80.12 | 5.67±0.023 | 91.61±1.45 | > 300 |

^an=3; standard deviation for three determinations

^bn=10; standard deviation for ten determinations

Table 3: Various Physical characteristics of prepared patches

| Formulation Code | Swelling index ^a | Percentage (%) | | In –vitro residence Time (hr) ^a |
|------------------|-----------------------------|----------------|---------------------|--|
| | | Moisture loss | Moisture absorption | |
| Placebo | 15.8 ± 1.04 | 10.67 ± 0.14 | 18.75 ± 0.23 | 2.15 ± 0.11 |
| F ₁ | 25.33 ± 2.98 | 9.62 ± 0.03 | 9.38 ± 1.53 | 3.25 ± 0.31 |
| F ₂ | 32.33 ± 4.76 | 10.08 ± 0.08 | 10.67 ± 2.18 | 3.12 ± 0.15 |
| F ₃ | 40.38 ± 3.05 | 12.61 ± 0.01 | 12.52 ± 1.18 | 2.51 ± 0.56 |
| F ₄ | 29.05 ± 4.12 | 5.18 ± 0.09 | 5.83 ± 2.53 | 3.48 ± 0.43 |
| F ₅ | 36.15 ± 2.10 | 6.42 ± 0.67 | 6.00 ± 1.66 | 3.30 ± 0.11 |
| F ₆ | 42.81 ± 1.45 | 8.31 ± 0.38 | 7.71 ± 2.73 | 3.05 ± 0.25 |
| F ₇ | 40.8 ± 3.01 | 2.76 ± 0.18 | 3.25 ± 3.52 | 4.13 ± 0.37 |
| F ₈ | 48.12 ± 2.54 | 3.35 ± 0.23 | 4.03 ± 1.79 | 3.71 ± 0.41 |
| F ₉ | 52.28 ± 1.32 | 4.73 ± 0.18 | 5.17 ± 1.31 | 3.25 ± 0.43 |

^an=3; standard deviation for three determinations**Table 4: Bioadhesive parameters of atenolol patch**

| Formulation code | Bioadhesive strength (g) ^a | Force of Adhesion (N) | Bond strength (Nm ⁻²) |
|------------------|---------------------------------------|-----------------------|-----------------------------------|
| Placebo | 4.48±0.10 | 0.043 | 545.3 |
| F ₁ | 3.05±0.67 | 0.029 | 418.7 |
| F ₂ | 2.72±1.30 | 0.026 | 272.4 |
| F ₃ | 1.61±0.95 | 0.015 | 221.8 |
| F ₄ | 4.75±0.32 | 0.046 | 567.3 |
| F ₅ | 3.30±1.48 | 0.032 | 431.5 |
| F ₆ | 2.63±0.80 | 0.025 | 257.5 |
| F ₇ | 5.35±0.21 | 0.052 | 690.3 |
| F ₈ | 4.24±1.25 | 0.041 | 506.2 |
| F ₉ | 3.75±0.18 | 0.036 | 463.8 |

^an=3; standard deviation for three determinations

Table 5: Water Vapour transmission rate through the patches at different time intervals

| Formulation Code | Day 1 [*] (10 ⁻³) | Day 3 [*] (10 ⁻³) | Day 7 [*] (10 ⁻³) |
|------------------|--|--|--|
| Placebo | 9.45±0.21 | 4.25±1.68 | 2.01±0.61 |
| F ₁ | 7.18±1.45 | 3.72±1.42 | 1.65±0.11 |
| F ₂ | 10.48±1.02 | 4.93±0.78 | 1.11±0.35 |
| F ₃ | 12.21±0.52 | 5.61±0.19 | 1.95±0.26 |
| F ₄ | 5.56±0.18 | 2.0±0.81 | 1.01±0.45 |
| F ₅ | 6.38±0.32 | 2.73±0.57 | 1.17±0.12 |
| F ₆ | 7.54±0.80 | 3.52±0.37 | 1.78±0.62 |
| F ₇ | 4.67±0.53 | 1.65±0.28 | 0.63±0.11 |
| F ₈ | 5.15±1.33 | 2.16±0.32 | 0.81±1.61 |
| F ₉ | 6.08±0.97 | 3.73±0.72 | 0.97±0.78 |

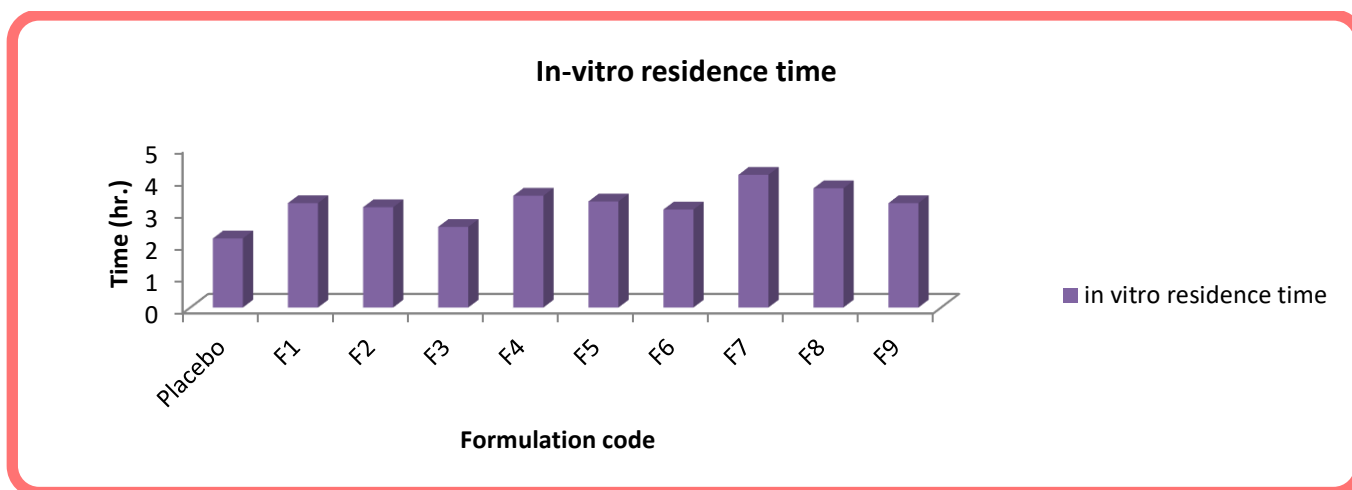


Fig:4 Graph showing In-vitro residence time of formulated patches.

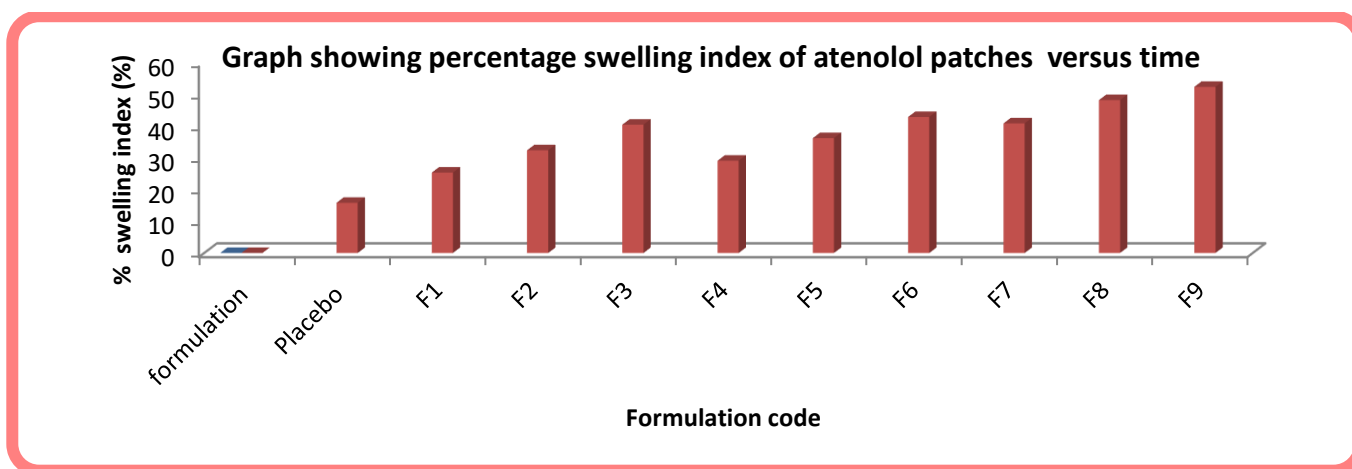


Fig -5: percentage swelling index of patches F1 to F9 containing atenolol

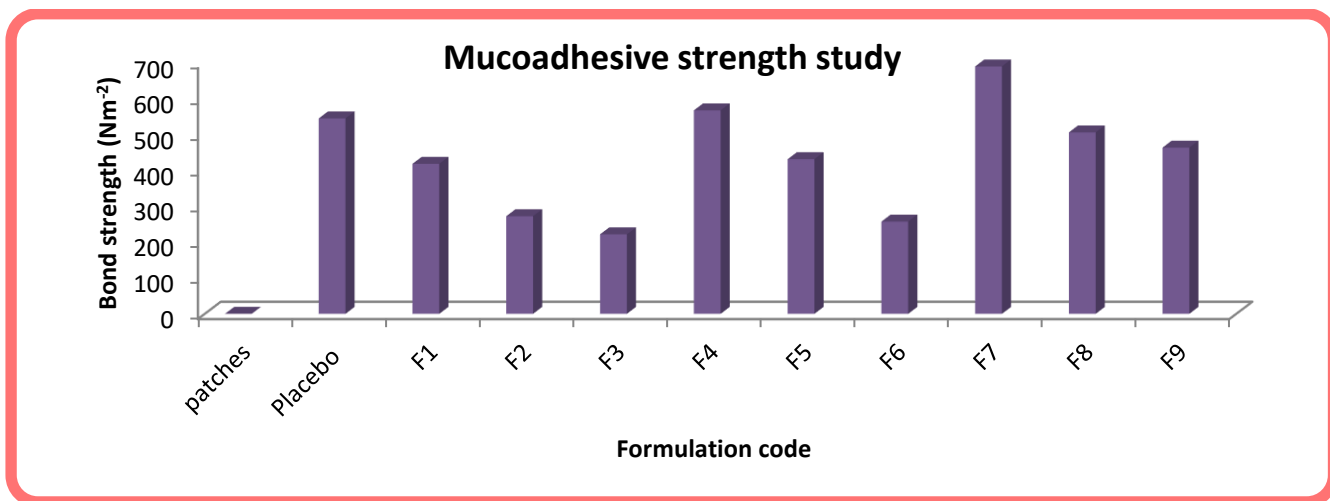


Fig- 6: Bond strength of patches F1 to F9 containing atenolol

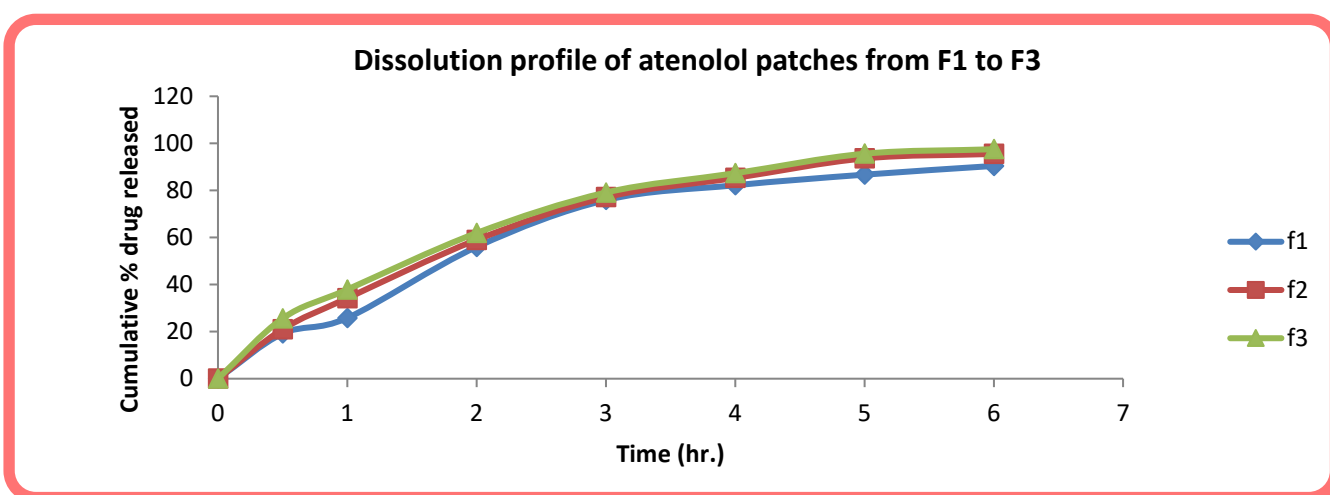


Fig- 7: Comparative dissolution profile of batches F1 to F3

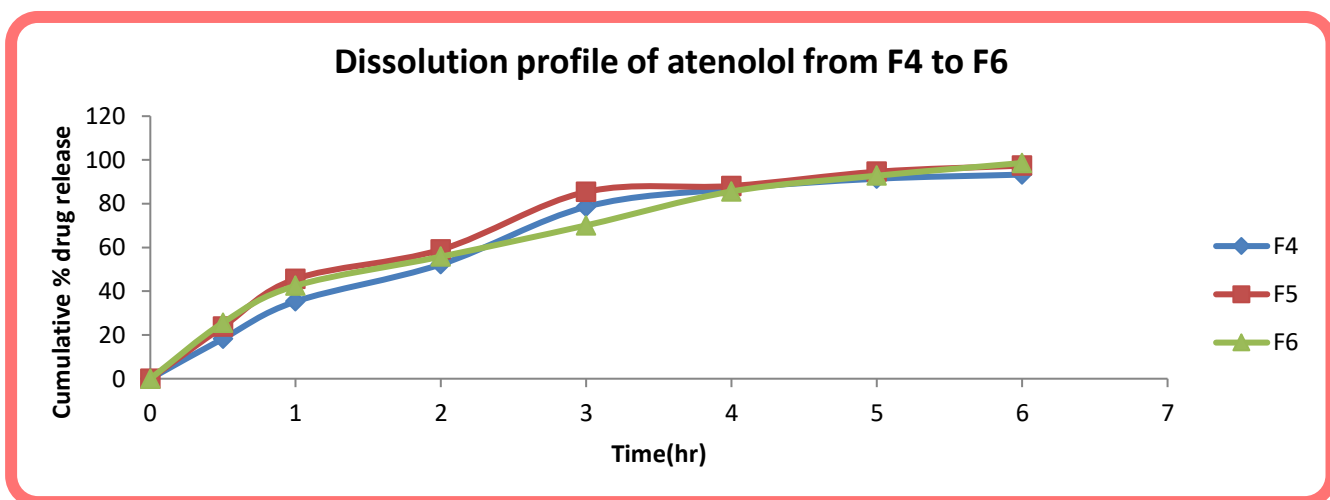


Fig-8: Comparative dissolution profile of batches F4 to F6

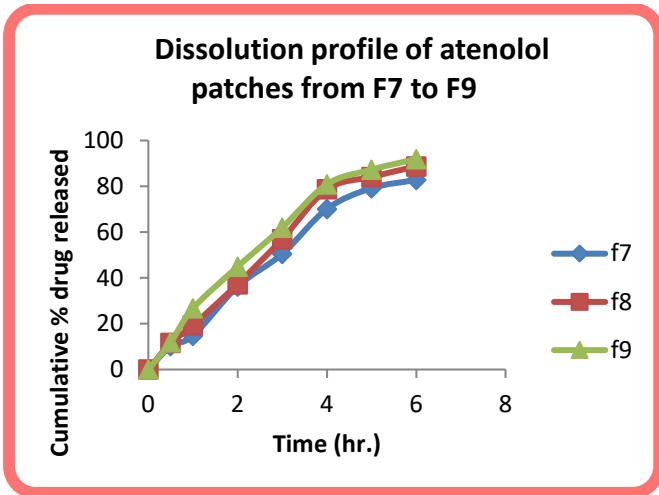


Fig. 9: Comparative dissolution profile of batches F7 to F9

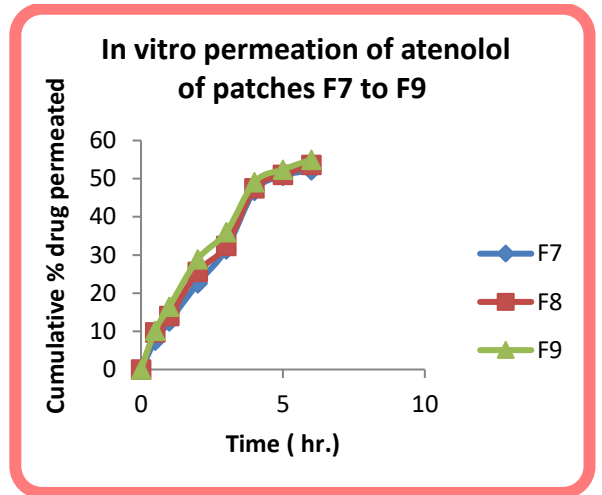


Fig. 12 : showing *in vitro* permeation of atenolol from patches F7 to F9.

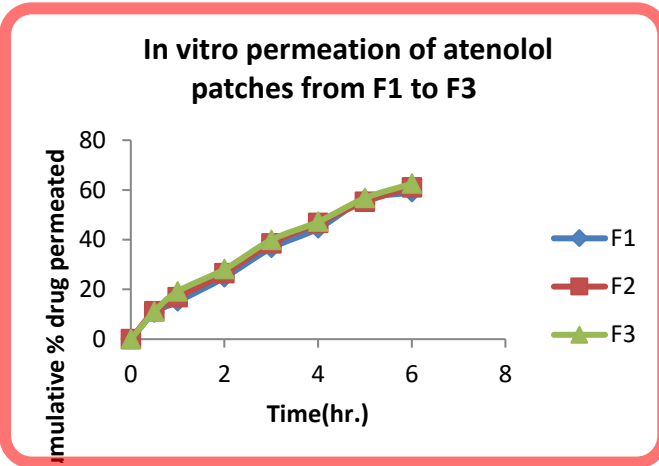


Fig. 10 : showing *in vitro* permeation of atenolol from patches F1 to F3.

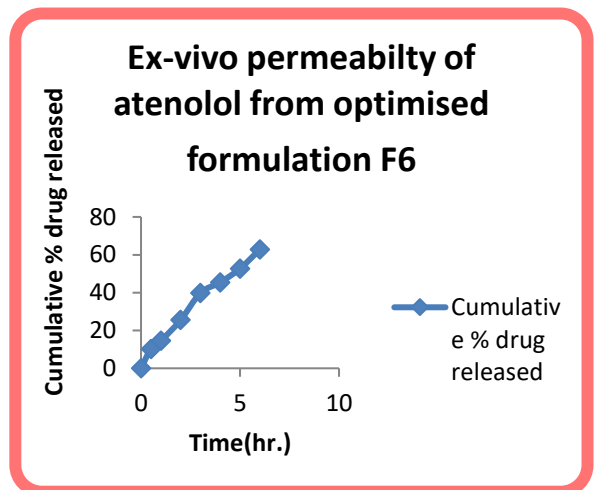


Fig. 13: Graph showing ex vivo permeability of atenolol from optimized formulation F6 in the phosphate buffer solution, pH 7.4 at 37°C

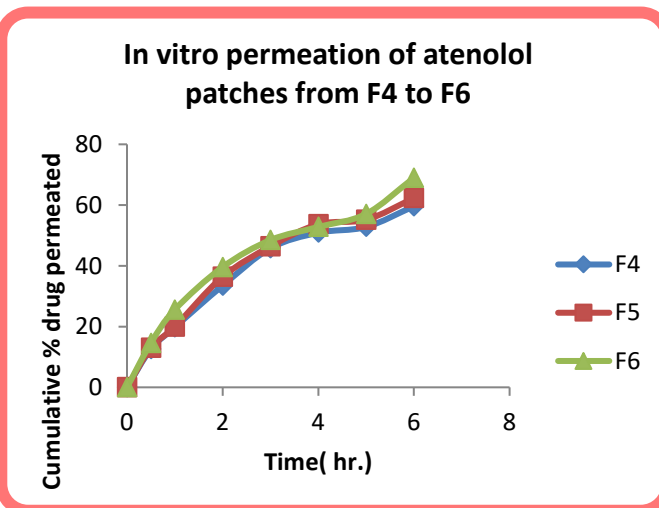


Fig. 11 : showing *in vitro* permeation of atenolol from patches F4 to F6.

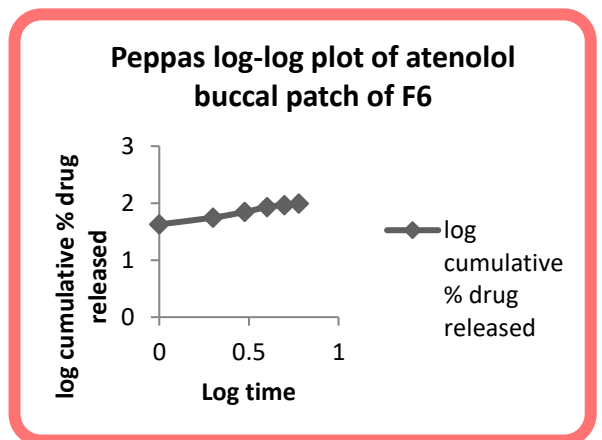


Fig. 14: showing atenolol release kinetic korsmeyer-peppas model of F6

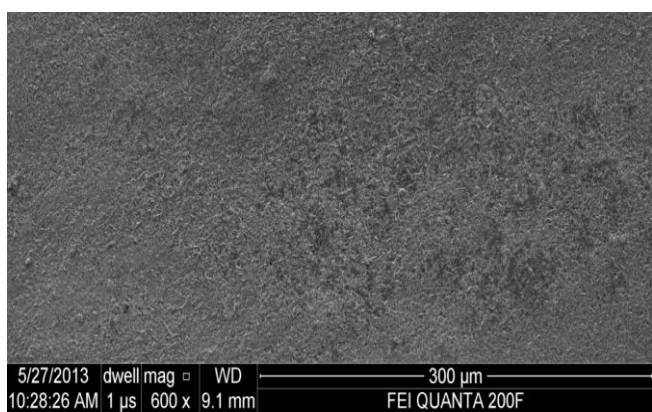


Fig- 15: (a), Scanning Electron Microscopy (SEM) of optimized formulation F6 under 600 × magnification

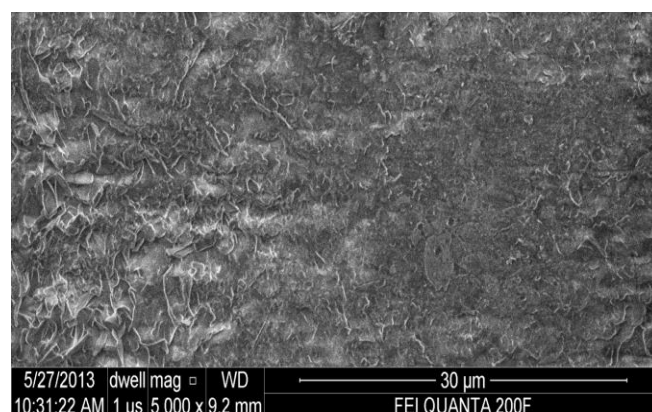


Fig- 15:(c) Scanning Electron Microscopy (SEM) of optimized formulation F6 under 5000 × magnification

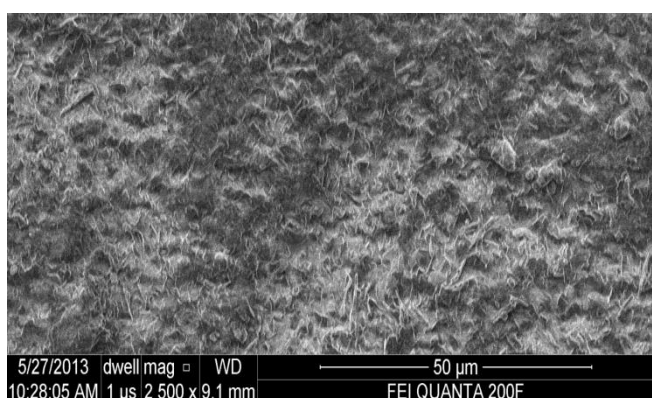


Fig- 15; (b) : Scanning Electron Microscopy (SEM) of optimized formulation F6 under 500 × magnification

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