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Original Article

Development and characterization of fast dissolving sublingual films containing Midazolam

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ABSTRACT

Midazolam, a short-acting benzodiazepine derivative is an upcoming therapeutic agent in the treatment and management of status epilepticus in pediatric patients. This study aims to formulate and evaluate the fast dissolving sublingual films of Midazolam with an aim to enhance the poor oral bioavailability due to first-pass metabolism. Pullulan, a natural polysaccharide produced from starch by the fungus, *Aureobasidium pullulans*, was used as the polymer in the formulation of films. We prepared fast dissolving films by solvent casting technique. Seven formulations were prepared by varying the concentration of pullulan and the plasticizer, PEG 400. Biophysical tests confirmed that there was no interaction between the drug and polymer. The films were evaluated for various physical parameters and for drug content and drug release. The films exhibited an acceptable range from 96.51-100.2% for drug content. The drug release was in the range of 95.1- 99.7% in 30 minutes for seven formulations. *In vivo* pharmacodynamic studies on male wistar rats suggested a four-fold increase in efficacy of the formulation compared with intraperitoneal dose of Phenytoin sodium. Our results describe an effective sublingual formulation of Midazolam that has potential therapeutic application in epilepsy.

Keywords: fast dissolving films, midazolam, pullulan, thin film drug delivery, sublingual films.

INTRODUCTION

There has been significant advancement in the field of drug delivery systems during the last decade. However, the traditional dosage forms may be inconvenient, sometimes impractical, for some patients. Geriatric and pediatric patients often face difficulty in swallowing liquid or chewing solid dosage forms. Many geriatric patients cannot administer the conventional formulations due to fear of choking [1]. It is also difficult for patients with sudden episodes of coughing or allergy, and those suffering from motion sickness to swallow solid dosage forms [2].

Fast dissolving films, a recent development in the field of drug delivery have gained importance in the current pharmaceutical industry due to uniqueness of their properties and advantages over conventional dosage forms. These films disintegrate in the saliva in less than a minute without the need for water and release the active ingredient [3]. These films have faster dissolution, quick absorption leading to a rapid onset of action and immediate relief [4]. Other benefits include excellent stability, patient compliance and enhanced bioavailability by surpassing the first pass metabolism. They are very convenient for geriatric, pediatric and patients suffering from psychiatric illnesses, as well as those who are travelling or do not have immediate access to drinking water. Fast dissolving films are very useful for uncooperative patients suffering with epileptic seizures. These films can be easily administered to such patients without having to force them to swallow a tablet.

Epilepsy is a set of chronic neurological disorders characterized by seizures. The seizures may be recurrent and unprovoked. The cause for the seizures may be unidentified but it mostly occurs due to brain trauma, stroke, and alcohol and drug misuse among others. Epileptic seizures occur as a result of excessive or hyper synchronous neuronal activity in the brain. Approximately 50 million people worldwide have epilepsy and about 80% cases of these are reported from developing countries [5].

Epilepsy is generally controlled, but not cured by medicines. Therefore, the application of fast dissolving dosage forms to treat the spontaneous

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nature of attacks will be very useful. It will ease the administration of the drug and be advantageous both for the patient as well as the physician. A faster acting dosage form will be highly advantageous as an anti-convulsant. Anti-convulsants are a diverse group of pharmaceuticals used in the treatment of epileptic disorders [6]. Most of these drugs act by causing sedation due to sodium or calcium channel blocking or by Gamma-amino butyric acid (GABA) enhancement. [7]

Midazolam is a short-acting benzodiazepine developed in the 1970's [7-9]. It is used for treatment of acute seizures, insomnia and for inducing sedation before any surgical procedures. Midazolam is a potent sedative, anxiolytic and anti-convulsant drug that is slightly bitter and has 27% oral bioavailability [8]. The current marketed preparations of Midazolam include tablets and parenteral products. The administration of Midazolam through the buccal or sublingual route is becoming increasingly popular for the emergency treatment of seizures in children [10]. The disadvantage of the oral route is the relatively large dose requirement due to the first pass metabolism of the drug. The sublingual route has the advantage of avoiding first pass metabolism and showing a rapid systemic absorption directly from the mucosal region [11, 12]. Here we report the development and characterization of sublingual films of Midazolam. We also tested the *in vivo* efficacy of these films and found them have a rapid onset of action.

MATERIALS AND METHODS

Materials: Midazolam was a kind gift from Sun Pharmaceuticals, Mumbai. Pullulan was a kind gift from Kumar Organic Products, Bangalore. PEG 400 was purchased from Merck Pvt. Ltd., Mumbai. Sodium citrate, citric acid and glycerol were purchased from Ranbaxy Fine Chemicals Ltd, New Delhi. All other chemicals and solvents were of analytical reagent grade and were used without further purification.

Compatibility studies: The compatibility studies were carried out at room temperature by Fourier Transform Infra-Red (FTIR) spectroscopy to determine any interaction between midazolam and the polymer, pullulan. The IR spectra of the drug alone and in combination with pullulan were taken. Physical mixture of drug and polymer was prepared and the sample was analyzed by FTIR Spectrophotometer (IRAffinity1, Shimadzu, Japan). Differential Scanning Calorimetry was performed using DSC-60. The instrument comprised of calorimeter (DSC 60), flow controller (FCL 60), Thermal analyzer (TA 60) and operating software TA 60 from Shimadzu Corporation, Japan. The samples were placed in aluminium pans and were crimped, followed by heating under nitrogen flow (25 ml/min). An empty aluminium pan was used as reference.

Preparation of fast dissolving films: Solvent casting method was used to prepare the fast dissolving films. A buffer of citric acid and sodium citrate (pH 3.4) in distilled water was prepared and drug was dissolved in 5 ml of the solution using a sonicator. This was labeled as solution A. 5 ml of distilled water was taken and weighed quantity (as per formulation code) of pullulan was soaked and dissolved in it Polyethylene glycol 400 (plasticizer) was added as per the requirement and the solution was stirred on a magnetic stirrer with further addition of sweetener and flavoring agent for up to three hours. This was labeled as solution B. Solution A was slowly added to solution B with constant stirring. Finally, the solution was set aside for removal of air bubbles and poured on pre-lubricated Petri plates (using glycerin) and dried in an oven for 2 hours at 60°C followed by air drying. The films were carefully removed after drying and cut into 2X2 centimeter square size. Films with any imperfections were not considered for further evaluation. The final samples of films were stored in a desiccator until further analysis.

Evaluation of films

Surface pH: A 2X2 cm^2 film was taken in a petri dish and a few drops of distilled water were sprinkled on the film. The electrode of the pH meter was brought in contact with the surface of the film and was allowed to equilibrate for 1 minute. The reading was recorded and the observations were carried out in triplicate for all formulations.

Thickness: The thickness of the film was measured using a dial caliper by folding the film four times and dividing it by four. All the measurements were carried out in triplicate for all the formulations and average with standard deviation was recorded.

Weight variation: Four-centimeter square of the film was cut at three different places from the casted film. The weight of each film was recorded and weight variation was calculated.

Folding endurance: Folding endurance was determined by repeated folding of the film at the same place till it breaks. The number of times the film is folded without breaking is taken as the folding endurance value.

Drug content: Drug content determination of the film was carried out by dissolving a film measuring 4 cm^2 in 100 ml of pH 6.8 phosphate buffer, using magnetic stirrer for one hour. The blank was taken as a blank film (without the drug) in 100 ml pH 6.8 phosphate buffer. The drug concentration was then

evaluated spectrophotometrically at λ_{max} of 216 nm. The determination was carried out in triplicate for all the formulations and average with standard deviation was recorded.

Tensile strength: Tensile strength is the maximum stress applied to a point at which the film specimen breaks. It was determined by holding a film of 5 X 2 cm^2 between two clamps 10 mm apart and the film was pulled by the clamp at a rate of 5mm/min. [13]

Percentage elongation: For the determination of the percentage elongation of the film, the distance between the tensile grips of the tensile strength testing machine was measured before and after the fracture of the film. The instrument used was TexturePro analyser CT V1.3 Build 15, Brookefield Engineering Labs Inc. Then the percentage elongation of the films was computed using the following equation:

$\%E = D_f\text{-}D_o / D_o \times 100$

Where,

%E = Percentage elongation

D_o = Distance between the tensile grips before the fracture of the film.

D_f = Distance between the tensile grips after the fracture of the film.

Disintegration time: *In vitro* disintegration time was determined visually in a petri dish containing 25 ml of phosphate buffer pH 6.8 with occasional swirling. The disintegration time is the time required for the film to break or disintegrate. All the measurements were carried out in triplicate for all the formulations.

***In vitro* dissolution studies:** The dissolution study was carried out using USP Type I dissolution apparatus and baskets were used for the study. The dissolution was carried out in 300 ml of pH 6.8 phosphate buffer maintained at 37±0.5°C at 50 rpm. 10 ml aliquots of samples were withdrawn at various time intervals and were replaced with the same volume of fresh phosphate buffer pH 6.8 maintained at 37±0.5°C. Midazolam in the samples was then analyzed spectrophotometrically at λ_{max} of 216 nm. The results were expressed as a mean of three determinations [14].

***In vivo* study:** Three groups comprising of six male Wistar rats of approximately 200g each were used for the experiment. All rats were maintained in a light-controlled room kept at a temperature of 22±2 ◦C and a relative humidity of 55±5%. They were divided into three groups. The first group was used as control and the second group was the standard group in which the rats were administered standard phenytoin (25mg/Kg) intraperitoneally. For sublingual administration in the test group, the film with calculated dose was placed beneath the tongue of the rats using a fine forceps. At first, MES (Maximal Electroshock Seizures) were induced in the rats that did not receive the formulation. An electroconvulsiometer was used for induction of epilepsy. The electrodes were clamped to both the ears of the rat and a current of 150 mA (milliampere) was given to the rat for 0.2 seconds and MES were induced. The different phases of epilepsy were noted and the time period for each stage was calculated. The same study was carried out in the standard and test group as well. The time of different epileptic phases in the three groups were noted and compared to observe the efficacy of the prepared formulation.

Short-term stability studies: Formulation F-1 was tested for stability for 90 days. The formulation was stored at room temperature (25±2°C) and at 40°C/75% RH for a period of three months when stored in a butter paper covered with an aluminium foil inside an airtight plastic bag. After 30, 60 and 90 days, studies for pH, folding endurance, drug content and drug release were carried out for F-1 formulation by the method discussed in sections 2.4.1, 2.4.4, 2.4.5, 2.4.9, respectively.

RESULTS

The IR spectrum of the pure drug was found to be similar to the standard IR spectrum of midazolam. The characteristic absorption peaks of midazolam were obtained at 1350.17 cm^{-1}indicating CN stretching, 767.67 cm^{-1}indicating C-Cl stretching, 1585.49 cm^{-1}indicating C=C aromatic stretching, 3197.98-3132.40 cm^{-1}indicating C-H aromatic stretching and at 1381.03cm^{-1}indicating C-F stretching. Compatibility studies of pure drug with pullulan were carried out prior to the preparation of films. IR spectra of pure drug and combination of drug and pullulan were obtained and are, shown in Table 2. All the characteristic peaks of midazolam were present in spectra thus indicating compatibility between the drug and polymer. It shows that there was no significant change in the chemical integrity of the drug. The heat flow as a function of temperature was measured for the drug, and for the drug –polymer physical mixture [15].The mixture showed sharp endotherms at 161.80°C and 28°C corresponding to melting point/transition temperature. There was no significant change in the melting endotherms of the physical mixture (midazolam + pullulan) compared to pure drug. The results of DSC studies are shown in Figure 1 and 2. Pure midazolam showed a sharp endotherm at 161.80°C corresponding to its melting point. The normal physiological pH of the sublingual region is 6.8. But it has the capability to tolerate pH between 3 and 10. The pH of all the formulations (F-1 to F-7) was found to be between 5.58-5.77. Thus, the formulated films are compatible with the buccal pH. The results are shown in Figure 5. The thickness of the film was measured using a dial

caliper and the reading was taken by folding the film four times and dividing it by four. The thickness of the films ranged from 0.15 to 0.21mm (Figure 5). This can also be attributed to the increasing concentration of polymer used in the formulations, as the area of the petri dish remained the same for all batches of formulations (F-1 to F-7). Four-centimeter square of the film was cut at three different places from the casted film. The weight of each film was recorded and weight variation was calculated. The mean weight of all films (F-1 to F-7) ranged from 61mg to 82.1mg, as shown in Figure 5. This variation can be attributed to the increasing concentration of polymer used as well as due to the varying concentrations of plasticizer used in each formulation. The folding endurance values of the seven formulations ranged from 163 to 380. This is due to the fact that as the concentration of the polymer in the film increases, the index of its physical strength reduces. It was observed that for formulation F-1, where the polymer concentration was 5%; the folding endurance value was 302, whereas, for formulation F-7, the folding endurance value was 163, due to high polymer concentration of 10%. The values of folding endurance for all formulations are given in Table 4. The percentage drug content of all the formulations was found to be in the range of 96.51-100.2% as shown in Table 3. The drug is uniformly distributed in the film. Thus, it can be concluded that there is no significant effect of the polymers on the drug content of the fast dissolving films. Tensile strength is an important aspect during the time of machine cutting and packaging of the films. The films need to be sturdy and should be able to resist the mechanical force of the cutting equipment without breaking/cracking. The values of tensile strength were in the acceptable range and are given in Figure 6. For the determination of the percentage elongation of the film, the distance between the tensile grips of the tensile strength testing machine was measured before and after the fracture of the film. The values for percentage elongation were in acceptable range and are given in Figure 6. The disintegration time for all formulations ranged from 22.3 sec to 49 sec taken as a mean of three observations. The disintegration time for formulation F-1 was the least whereas F-7 showed maximum disintegration time. This can be attributed to the concentration of polymer used, which was 5% and 10%, respectively (Table 3). The percentage cumulative drug release of formulations F-1 to F-7 after 30 minutes ranged from 95.09% to 99.67%. The percent cumulative drug release for F-1 to F-7 is given in Table 4. Maximum drug release was observed in formulation F-1 after 30 minutes. The reason attributed for a higher release is the lesser concentration of polymer employed in that formulation (500 mg). A comparative representation of the percentage cumulative drug release of all formulations is given in Figures 3 and 4. *In vivo* pharmacodynamic studies revealed a fast onset of action of 7 minutes and better efficacy of midazolam when compared with standard phenytoin injection. This was evident by the reduction in the time duration of various epileptic phases (Table 5). Short-term stability studies indicated that the formulations were stable at room temperature (25±2°C) and at 40°C/75% RH for a period of three months when stored in a butter paper covered with an aluminium foil inside an airtight plastic bag.

DISCUSSION

Midazolam, a fast acting benzodiazepine is one of the drugs used in the treatment of refractory status epilepticus and bipolar disorders. It has a property of rapidly penetrating the blood-brain barrier and exerts a short duration of action. However, it may lead to tachyphylaxis on prolonged usage [16]. Brevoord J.C. et.al analyzed a treatment protocol based on midazolam and phenytoin clinically, where midazolam proved to be a better alternative over phenytoin in the treatment of refractory status epilepticus [17]. In another study, Kumar et.al [18] tested intravenous midazolam for the treatment of refractory status epilepticus. Rivera et.al [19] studied the effect of midazolam in the treatment of status epilepticus in children and no adverse reactions were reported. Also, Koul et.al [20] attempted the use of continuous infusion of midazolam in the treatment of status epilepticus and observed no transient desaturation. Mashru et.al [21] formulated fast dissolving sublingual films containing Salbutamol sulphate, with polyvinyl alcohol as the polymer, mannitol as filler and glycerol as plasticizer for acute asthma attacks. The study summarizes the amounts of excipients needed for an optimal fast release film that produces the desired physiological effect. Choudhary et.al [22] prepared fast dissolving films containing Levocetrizine using hydroxypropyl beta cyclodextrin in 1:1 molar ratio. Pullulan (2% w/v), xanthan gum (0.4%w/v), propylene glycol (0.2% w/w) and tween 80 (0.1% w/w) and the above complex were dispersed in 25 ml of water and solvent casting method was employed. Parameters such as appearance, weight, tensile strength, content uniformity and disintegration time were studied. *In vitro* and *in vivo* studies were also carried out. The *in vitro* dissolution profile suggests rapid disintegration in which most of the drug dissolved within 90 seconds after insertion into the medium. Sprague-Dawley rats were used to study pharmacokinetic properties of the film in comparison with the pure drug solution. The

current study satisfactorily fulfills the shortcomings of conventional dosage forms in terms of absorption, drug release and the bioavailability of the drug. Furthermore, the results of our study suggest a promising sublingual formulation of midazolam that is fast acting, convenient and effective in the prevention and control of status epilepticus. The formulation shows effective drug release and a fast onset of action of seven minutes, as observed in the *in vivo* experiments on rats. The advantages of this study include an effective and patient friendly dosage form when compared to the conventional tablets and injections. This formulation will be compliant with pediatric and geriatric patients and in those with swallowing disorders. Future studies will focus on taste evaluation studies in human volunteers, and long-term stability studies as well as *in vitro-in vivo* correlation.

CONCLUSIONS

Our study demonstrates that fast dissolving sublingual films containing midazolam can be prepared using pullulan as the film-forming polymer and PEG 400 as the plasticizer. The films were translucent in appearance without cracks or imperfections (Figure 7) and exhibited good mechanical properties as well as acceptable drug content and drug release. Formulation F-1 showed the fastest *in vitro* disintegration time of 22 seconds out of the seven formulations, and a good stability for three months at room temperature as well as 40°C/75% RH. Furthermore, formulation F-1 showed greater efficacy *in vivo* in comparison to the standard drug phenytoin, suggesting midazolam as a promising therapeutic agent in the management and treatment of status epilepticus.

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Table 1: Composition of Formulations F-1 to F-7

Formulation code	Midazolam (mg)	Pullulan (mg)	PEG 400 (ml)	Aspartame (mg)	Water (ml)	Vanillin (ml)
F1	90	500	0.45	90	10	0.04
F2	90	750	0.25	90	10	-
F3	90	750	0.35	90	10	-
F4	90	750	0.45	90	10	0.04
F5	90	1000	0.25	90	10	-
F6	90	1000	0.35	90	10	-
F7	90	1000	0.45	90	10	0.04

Table 2: FTIR spectra of pure drug and drug-polymer mixture

Functional Groups	Pure Drug	Drug + Polymer
C-Cl	767.67 cm^{-1}	769.60 cm^{-1}
C=C (Aromatic)	1585.49 cm^{-1}	1585.49 cm^{-1}
C-H (Aromatic)	3197.98-3132.40 cm^{-1}	3076.46-3010.88 cm^{-1}
C-F	1381.03 cm^{-1}	1375.25 cm^{-1}

Table 3: Percentage drug content and *in vitro* disintegration time of all formulations

Formulation Code	Percentage drug content of films*	*In vitro* disintegration time of films*(sec)
F-1	99.76±0.04	22.3±1.3
F-2	99.06±0.11	26±3
F-3	100.2±0.18	34±2
F-4	97.67±0.09	32±4
F-5	96.51±0.10	33±2
F-6	98.13±0.17	40±1

* Data are expressed as mean ± SD (n=3).

Table 4: Percentage cumulative drug release of all formulations

Time (min)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	Pure Drug
0	0	0	0	0	0	0	0	0
2	43.95	37.67	41.86	37.67	33.49	33.49	35.58	79.2
5	84.21	79.95	82.09	82.05	79.91	75.72	79.93	100
10	89.33	82.93	85.09	85.05	82.88	80.74	82.91	-
15	92.4	90.12	92.3	90.16	87.98	83.72	88	-
30	99.67	95.28	97.49	97.42	97.3	95.09	97.33	-

Table 5: Time duration of epileptic phases in rats

Stages of Epilepsy	Time taken in control group* (sec)	Time taken in standard group* (sec)	Time taken in standard group* (sec)
Flexion	5.4	Not observed	Not observed
Extension	8.23	3.72	1.29
Clonus	6.31	4.24	1.03
Stupor	12.66	10.18	3.54
Recovery	Recovered	Recovered	Recovered

*The above readings are a mean of six observations.

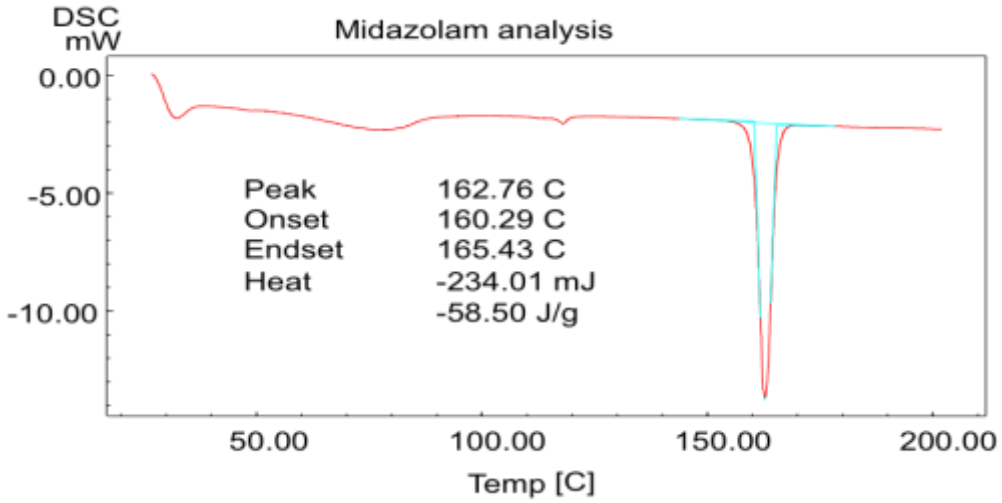


Figure 1: DSC studies of pure midazolam.

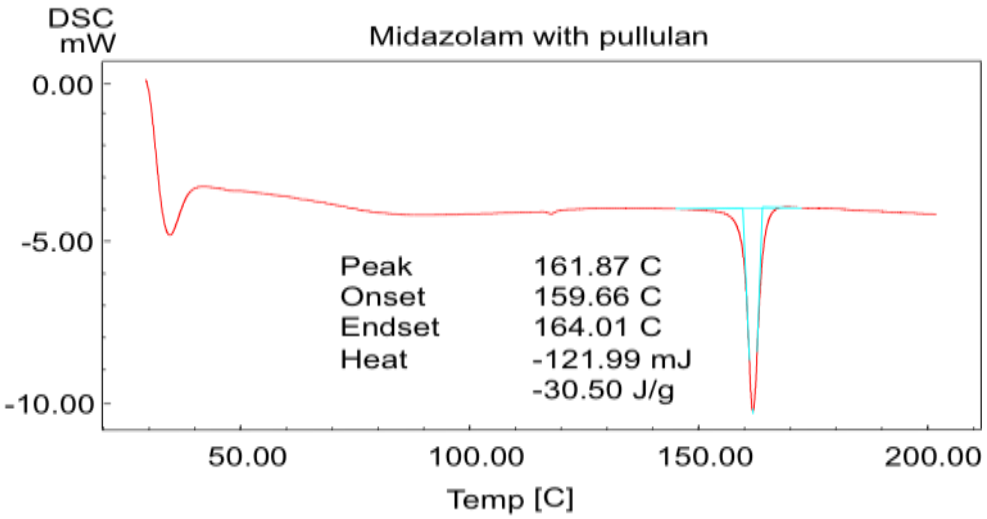


Figure 2: DSC Studies of physical mixture (midazolam + pullulan).

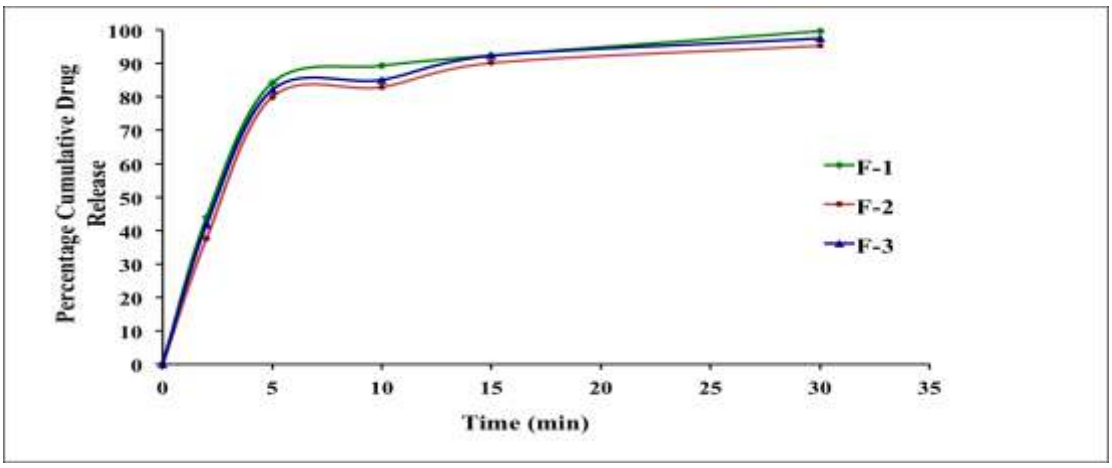


Figure 3: Comparative *in-vitro* dissolution profile of formulations F-1 to F-3.

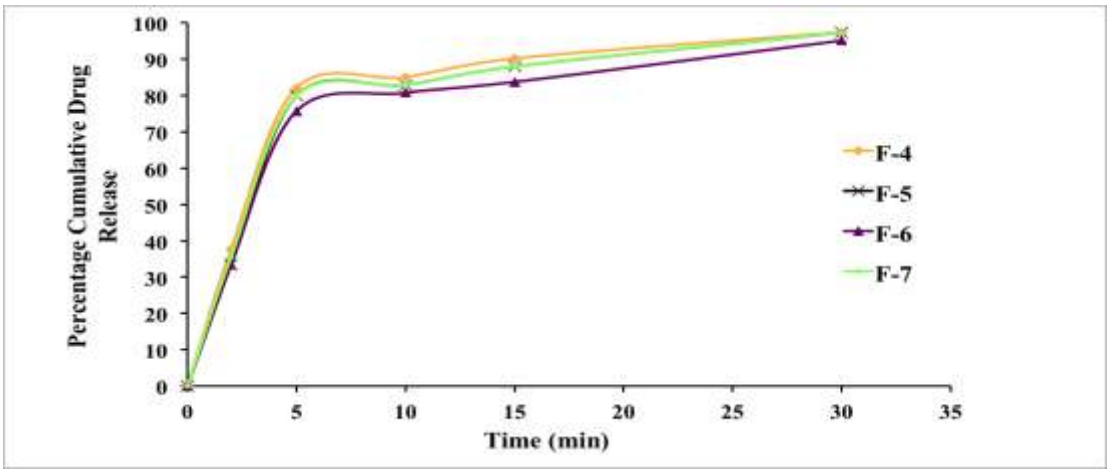
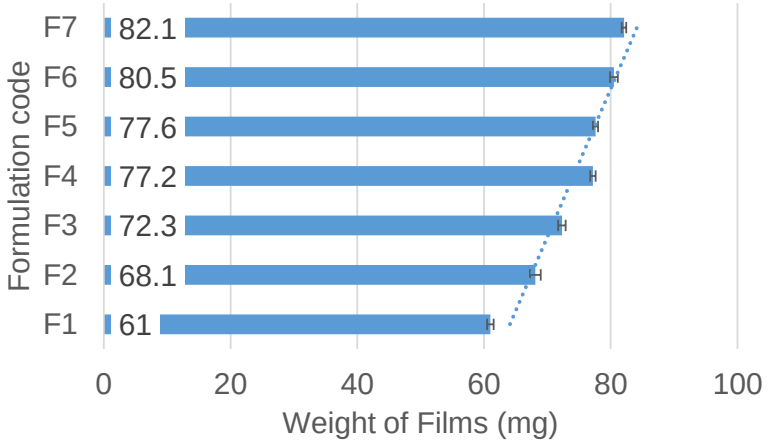
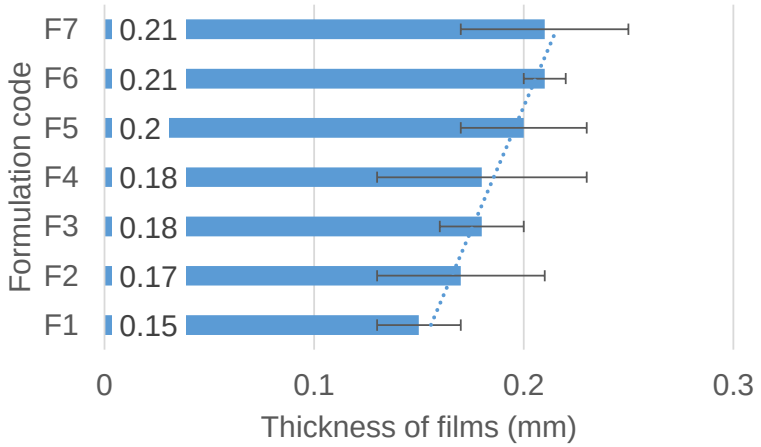


Figure 4: Comparative *in vitro* dissolution profile of formulations F-4 to F-7.





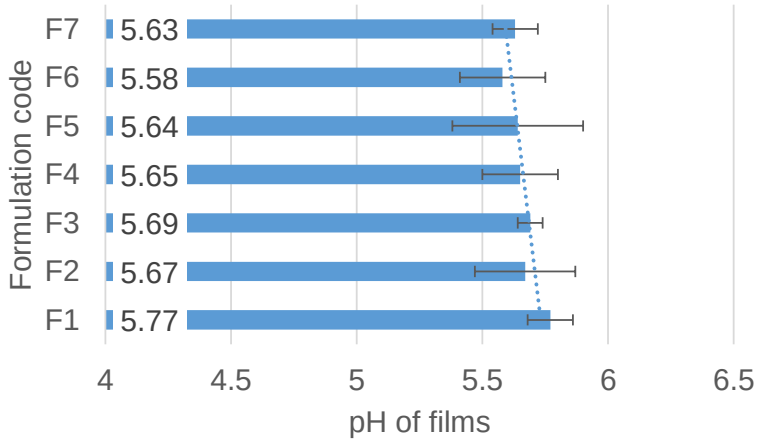


Figure 5: Comparative weight, thickness and pH of formulations F-1 to F-7.

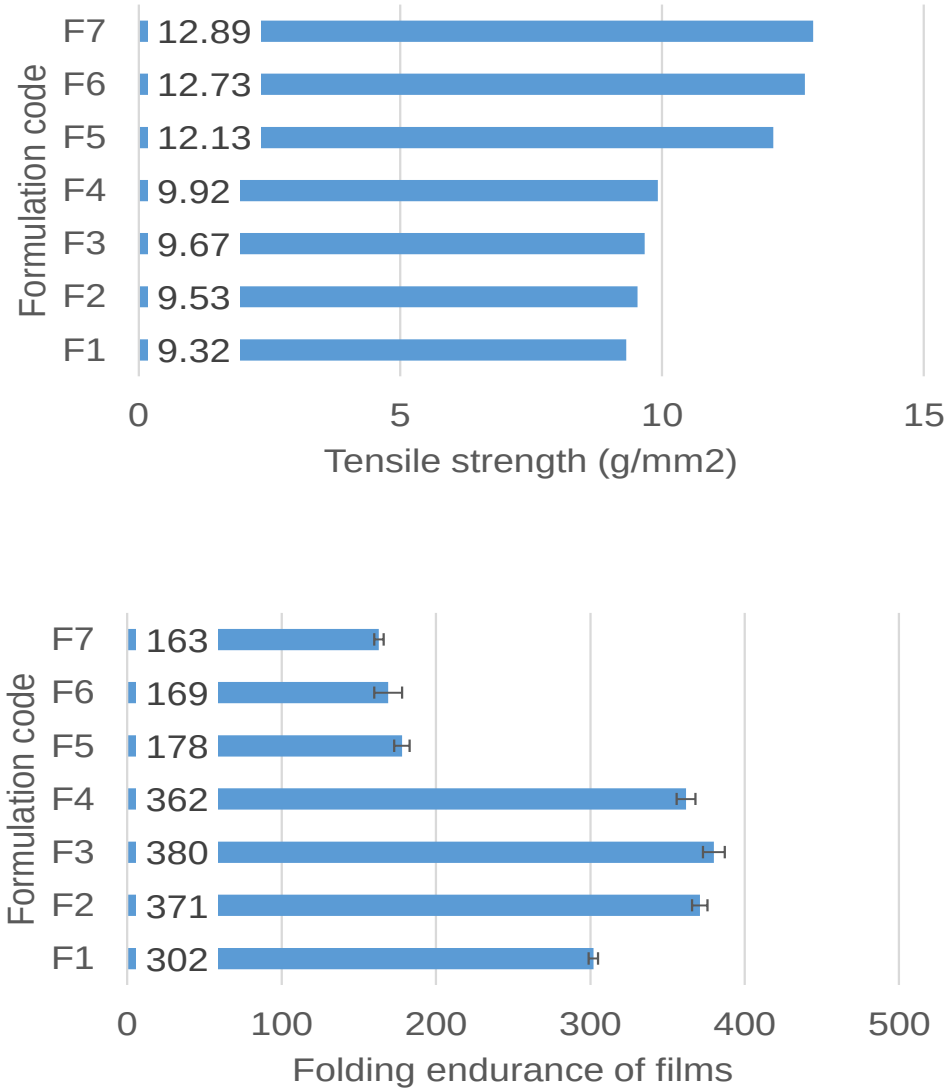


Figure 6: Comparative tensile strength and percentage elongation values for formulations F-1 to F-7.

Figure 7: Optimized formulation F-1

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