http://doi.org/10.25130/tjphs.2024.18.2.2.12.19

IRAQI Academic Scientific Journals

Tikrit Journal of Pharmaceutical Sciences

ISSN: 1815-2716 (print) -- ISSN: 2664-231X (online)

Journal Home Page: https://tjphs.tu.edu.iq -- Email: tjops@tu.edu.iq

TJPHS

Preparation and In-vitro Evaluation of Tizanidine oral Film

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Keywords:
Tizanidine,
Oral film,
Polyvinyl alcohol,
Dissolution

Article history:
-Received: 02/11/2024
-Received in revised: 29/11/2024
-Accepted: 01/12/2024
-Available online: 25/12/2024

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Citation:
Fadhel AY. Preparation and In-vitro Evaluation of Tizanidine oral Film. Tikrit Journal of Pharmaceutical Sciences 2024; 18(2):12-19.
http://doi.org/10.25130/tjphs.2024.18.2.2.12.19

Abstract

Fast-dissolving oral thin film is a novel and most advanced form of solid dosage form that dissolves or disintegrates in 1 minute when put in the mouth without water or chewing. Tizanidine hydrochloride is frequently used to treat back pain, multiple sclerosis, spastic diplegia, and specific spinal or central nervous system ailments and it was prepared as oral film for produce rapid therapeutics effect .Solvent casting was the procedure used to prepare the mouth-dissolving films. Eight formulas of the tizanidine were prepared by using different concentrations of HPMC E15 and polyvinyl alcohol (PVA).

The effect of the type and concentration of the polymer was evaluated in all the formulations was evaluated for surface pH, weight uniformity, folding endurance, disintegration time, in-vitro dissolution studies. The formulation F2 was found to be an optimized formulation. It showed good results for all evaluation parameters such as weight variation 15.9±0.23 mg, surface pH 4.38, folding endurance 106, disintegration time 40 sec, and in-vitro dissolution study 100 % at the end of 4 min. From all of the observations can conclude that the formulation F2 shows better results.

تحضير وتقييم شرائح تيزانيدين عن طريق الفم في المختبر

احمد يوسف فاضل

فرع الصيدلانيات، كلية الصيدلة، جامعة تكريت، تكريت، العراق

الخلاصة

الشرائح الرقيقة الفموية سريعة الذوبان هي شكل جديد وأكثر تقدمًا من أشكال الجرعات الصلبة التي تذوب أو تتفكك في دقيقة واحدة عند وضعها في الفم بدون ماء أو مضغ. كثيرا ما يستخدم تيزانيدين هيدروكلوريد لعلاج آلام الظهر، والتصلب المتعدد، والشلل المزدوج التشنجي، وأمراض معينة في العمود الفقري أو الجهاز العصبي المركزي، وقد تم إعداده كشرائح عن طريق الفم لإنتاج تأثير علاجي سريع. كان صب المذيبات هو الإجراء المستخدم لتحضير الشرائح التي تذوب الفم. تم تحضير ثمانية صيغ من التيزانيدين باستخدام تراكيز مختلفة من HPMC E15 وكحول البولي فينيل (PVA).

تم تقييم تأثير نوع وتركيز البوليمر في جميع المستحضرات وتم تقييم درجة الحموضة السطحية، وتجانس الوزن، وتحمل الطي، وزمن التفكك، ودراسات الذوبان في المختبر.تبين ان الصيغة F2 لتكون صياغة محسنة. أظهرت نتائج جيدة لجميع معايير التقييم مثل اختلاف الوزن 15.9 ± 0.23 ملجم، الرقم الهيدروجيني للسطح 4.38، تحمل الطي 106، زمن التفكك 40 ثانية، ودراسة الذوبان في المختبر 100٪ في نهاية 4 دقائق. من جميع الملاحظات يمكن أن نستنتج أن الصيغة F2 تظهر نتائج أفضل

الكلمات المفتاحية: تيزانيدين، الشرائح الفموي، كحول البوليفينيل، الذوبانية

Introduction:

One of the most popular medication administration methods is oral since it is more affordable, convenient, and easy to administer, increasing patient compliance. The oral route presents challenges due to the inability of older and pediatric patients to swallow and their fear of choking. Research focused on compliance and patient comfort has led to the development of safer and more modern drug delivery methods [(1)]. Due to the possibility of using the ultra-structural characteristics of the oral mucosa to deliver biologically active medications topically or systemically, which have high pharmacological efficacy and site-specificity, these medications have garnered more attention. However, there is currently no safe, efficient, or non-invasive way to administer them.Oral transbuccal drug administration is becoming a more viable option than traditional ways because it has several benefits, including increased bioavailability, which requires smaller doses of the medication and results in less dose-related side effects than more traditional routes [(2, 3)]. A rather thick, dense, multilayered mucosal membrane with a high degree of vascularization lines the oral cavity. In theory, the epithelium of the mouth cavity and the skin are comparable, but there are several notable differences, such as keratinization and the protective and lubricating mucus that is distributed across the oral surface [(4)]. The terms of fast-dissolve pharmaceutical drug delivery are currently of particular interest. In recent years, dissolvable oral thin films (OTFs) have transitioned from the confection and oral care sectors into a unique and extensively embraced format for the delivery of vitamins and personal hygiene goods by consumers [(5)].

Businesses that had previously developed polymer coatings with active pharmaceutical ingredients (APIs) for transdermal medication delivery seized the chance to transfer this expertise to OTF forms and are in the early- to mid-development stages for prescription drugs [(6)].

Tizanidine: Tizanidine acts on the central nervous system and relaxes muscles. It is a myotonolytic medication used to treat spasticity in people with brain or spinal injuries. It functions as a central alpha-2 adrenoceptor agonist. It is an antispastic medication with a more favorable tolerance profile and an efficacy similar to baclofen [(7)].

Material and method

Preparation of oral thin film

Utilizing the solvent casting method, various concentrations of HPMC E15 and polyvinyl alcohol (PVA) are used to create the fast-dissolving oral film of tizanidine. Initially, distilled water is used to dissolve the HPMC E15 and PVA to prepare an aqueous solution. Tizanidine is added to the aqueous solution then added to the above solution followed by addition of the sweetener and plasticizer (poly ethylene glycol and glycerin).After the solution was cast onto a Petri plate, it was dried for 24 hours at 45 ^{0}C in a hot air oven. Next, the film was taken off the surface and sliced into the required dimensions of 2*2 cm for an equivalent dosage 2mg of tizanidine [8].

Preparation of calibration curve of tizanidine HCl

Using a Shimadzu 1800 UV visible spectrophotometer, the calibration curves for tizanidine HCl were prepared in phosphate buffer pH 6.8. A precisely weighed 50 mg of tizanidine hydrochloride was added to a 50 ml volumetric flask, and the volume was increased by adding phosphate buffer (pH 6.8) to prepare a 1000µg/ml stock solution. From the stock solution serial dilutions of 10, 6.6,5,4 µg/ml were prepared [9].

Folding endurance The film's physical stability throughout production, packaging, and use is represented by its folding endurance and tensile strength, which are both correlated with the film's flexibility. A film was forcibly folded across the middle many times to hand measure it. The value of folding endurance was determined by counting how many folds on the same crease were needed to cause a crack in the material [10].

Folding endurance

The folding endurance values of all the formulations' films are listed in Table 2. It was found that the folding endurance ranged from 57 to 144.Which may be the result of strong hydrogen bonds forming between the polymer and the plasticizer, giving the product flexibility to survive rupture [15]. The average folding endurance of all films is shown in Fig 2**.**

Weight Variation

Each of the ten samples of each formulation had its unique weight ascertained. The weighted average was calculated [11].

Surface pH The film was put in a Petri dish to evaluate this test. It was then soaked for 30 seconds with 0.5ml of phosphate buffer. After contacting the formulation's surface with the pH meter's electrode and letting it acclimate for one minute, the pH was measured[12].

In-vitro disintegration time The film strip (2 × 2 cm^2) was placed in a 6 cm diameter Petri dish with 25 ml of pH 6.8 phosphate buffer to determine the disintegration time. The amount of time needed for the film to completely dissolve was noted. Every measurement was made three times and the average results were given [13].

In-vitro release study Using a USP II paddle dissolution equipment, the in-vitro dissolution test was conducted. The suitable-sized (2 × 2 cm2) films were cut and added to the dissolving medium. A 300 ml freshly made phosphate buffer (pH 6.8) was used as the dissolving media, which was agitated at 50 rpm and kept at 37 ± 0.5 ºC. At time intervals (1 minute), 5 ml samples were removed and replaced with new media. The samples were examined under a UV lamp at 320 nm (λ max) [14].

Results and discussion

Construction of calibration curve

Figure 1 shows the developed calibration curves of TZN in phosphate buffer pH 6.4. When the absorbance was plotted against the concentration, a straight line was formed with a large coefficient of determination. According to this, the calibration curve over the concentration range complies with Beer's law.

Weight Variation

The average weight variation values of all the formulations' films are shown in Table 2. It was found that the weight variance ranged from 15.3 to 23.4 mg. The formulations were confirmed to meet the weight variation criterion in accordance with USP guidelines. A product's weight variation with a low standard deviation indicates it is repeatable. The formulations were verified to meet the weight variation criterion in accordance with

USP regulations[16].Average weight variations of all films are shown in the Fig 3.

Surface pH

The objective of measuring the surface pH of TZN fast-dissolving oral thin films was to explore the potential for any in vivo adverse reactions. The surface pH should be kept as close to neutral as possible since an acidic or alkaline pH may irritate the oral mucosa. Average surface pH ranges from 4.3-6.1 [17].

Disintegration time

As shown in figure 4, it was found that the in vitro disintegration times for each formulation ranged from 40 to 180 seconds. HPMC E15 demonstrated superior film-forming ability, tensile strength, and disintegration time [18].

In vitro dissolution study

Figure 5 and figure 6 shows the dissolution profiles of TZN from the prepared films. All films promptly released their entire drug content within 2−6 min. For F3, and F4 formulations, TZN gradually released at 6 min about 84%. Both F3 and F4 formulation containing higher concentration of HPMC K15M showed slower release rate compared to the other formulations (F1 and F2). A film's thickness rises when its HPMC concentration increases because it produces a greater swelling ratio. It follows that HPMC E15 layer can lessen drug diffusion through other polymeric material, as other research teams utilizing HPMC-based oral films have also confirmed [19].Formulas of HPMC (F1, F2, F3, and F4) showed higher drug release than PVA formulas (F5, F6, F7 and F8) but not significant, this is due to the swelling property of this PVA polymer which makes a gel-like layer on the surface of the film upon contact with aqueous media lead to prevent penetration of water to the film and delay drug release, this swelling property increased with increasing of the polymer concentration and more delay in drug release [20].

The results indicated that altering the type of plasticizer had no significant impact ($p>0.05$) on the in vitro dissolving film DT. This could be because the two plasticizers (PEG400 and glycerin) improved the disintegration time by allowing fluids to penetrate the strip. Since plasticizers change the densely packed chains of HPMC texture by forming a polymer structure with more pores and less density that breaks at a lower force, this is another reason why HPMC releases drugs more quickly than PVA polymer [21]. The formula F2 is selected as the best formula since it has very transparent visual appearance, good folding endurance (106), acceptable pH value (4.38), least disintegration time (40 sec.), and 100% drug release within four minutes.

Conclusion

The orally disintegrating film is an emerging oral dosage form, that is elegant, easily portable, and does not require water for swallowing. In this study the tizanidine was good fabricated to prepare it as eight oral films by solvent casting method for produce rapid therapeutics effect.

The formulation F2 was found to be an optimized formula. It shows the disintegration time 40 sec, and in-vitro dissolution study 100 % at the end of 4 min, so it can conclude that the tizanidine oral film is a good strategic method for produce rapid therapeutic effect by rapid dissolve in oral cavity.

Acknowledgements

The author would like to acknowledge the University of Tikrit, College of Pharmacy for providing laboratory and equipment without which most of this work would not be possible.

Table 1: Formulation of Different TZN Oral Film

No.formulas	TZN (mg)	HPMCk15 (mg)	PVA (mg)	PEG 400 (mg)	glycerin (mg)
1	**2**	**400**		**120**	
2	**2**	**400**			**129**
3	**2**	**600**		**120**	
4	**2**	**600**			**120**
5	**2**		**400**	**120**	
6	**2**		**400**		**120**
7	**2**		**600**	**120**	
8	**2**		**600**		**120**

Table 2: Evaluation of Folding Endurance, Weight Variation, Disintegration Time, and Surface pH, of TZN Oral Thin Films Formulation

No. Formulas	Folding endurance	Weight variation(mg)	Surface pH	Disintegration time(sec)
1	**98**	**15.3 ± 0.1**	**4.6**	**70**
2	**106**	**15.9 ± 0.23**	**4.38**	**40**
3	**130**	**23.2± 0.2**	**4.36**	**110**
4	**144**	**22.4± 0.3**	**4.57**	**100**
5	**57**	**15.5± 0.15**	**6.1**	**180**
6	**68**	**16.4 ± 0.12**	**5.68**	**135**
7	**79**	**23.4± 0.32**	**5.52**	**165**
8	**72**	**21.9 ± 0.22**	**5.17**	**137**

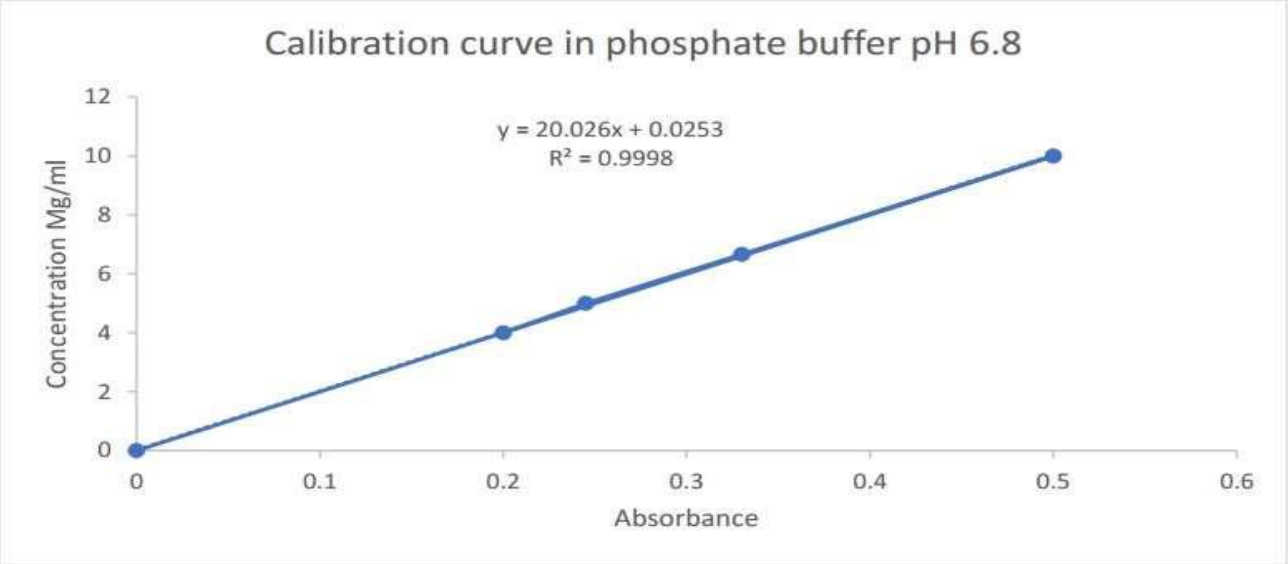

Figure 1: Tizanidine calibration curve in phosphate buffer pH 6.4

Figure 2: Comparative Folding endurance of all the formulations 3.3. Weight Variation

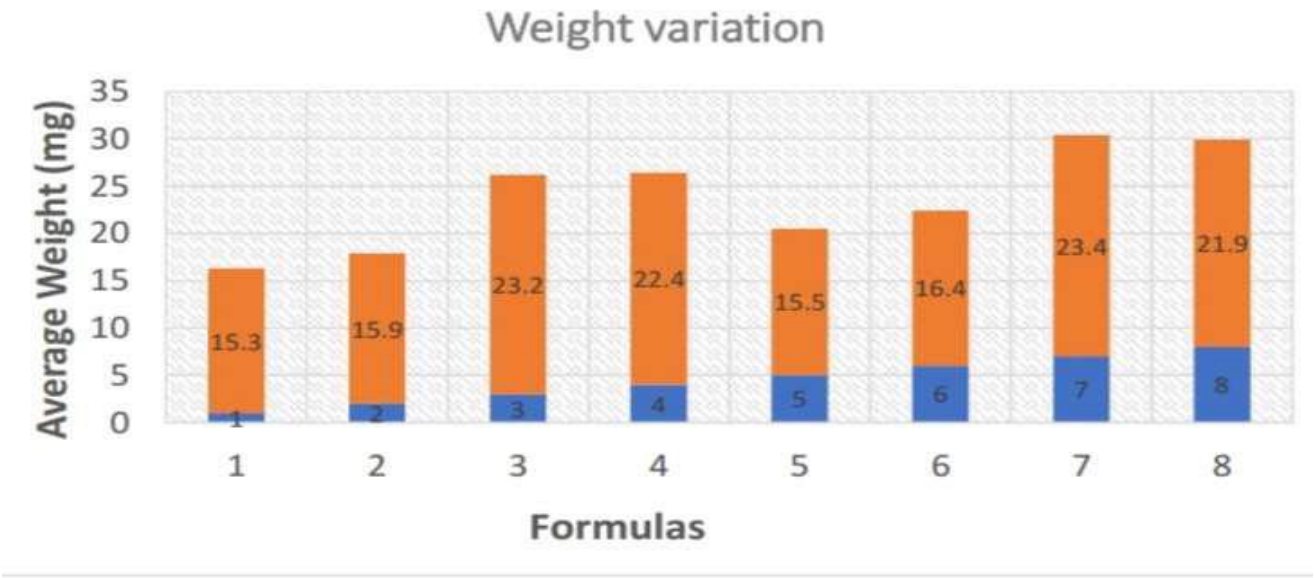

Figure 3: Comparative Weight Variation of all the formulations

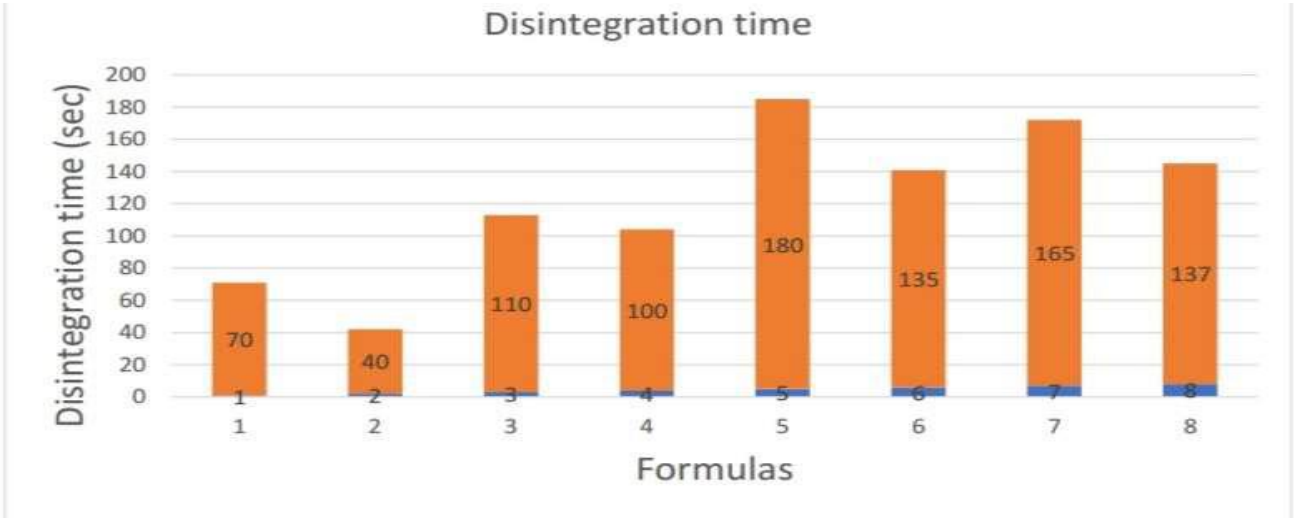

Figure 4: Comparative disintegration time of all the formulations.

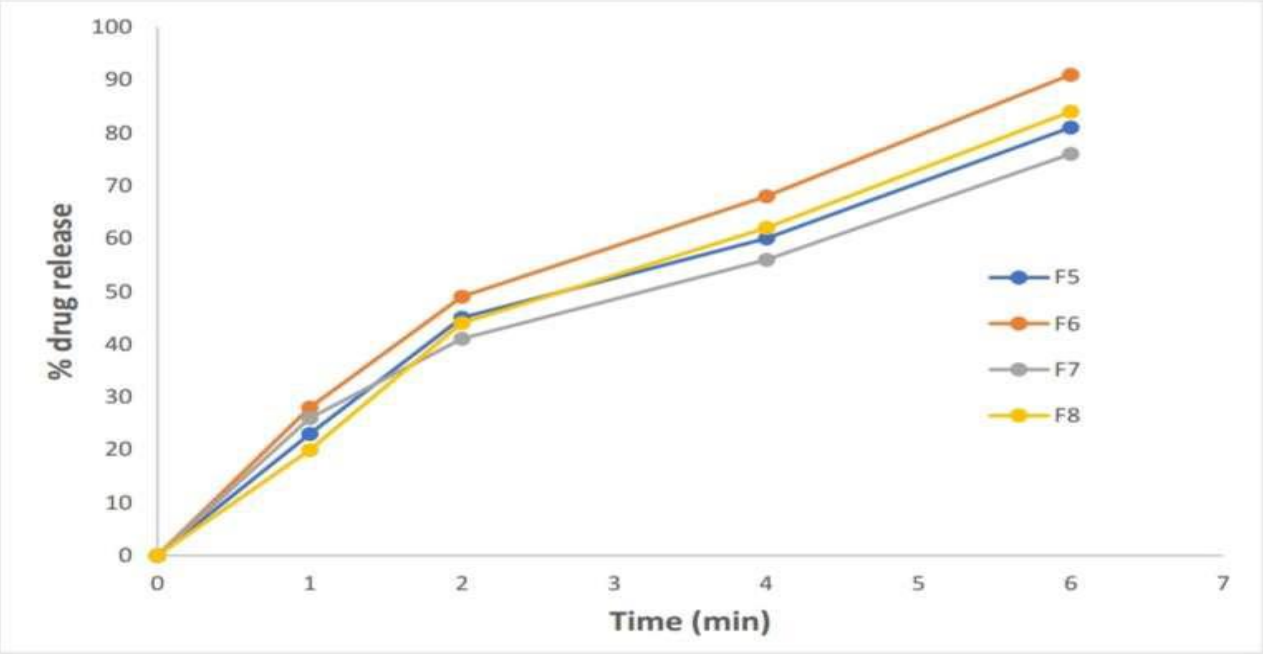

Figure 5: in vitro drug release from HPMC E15

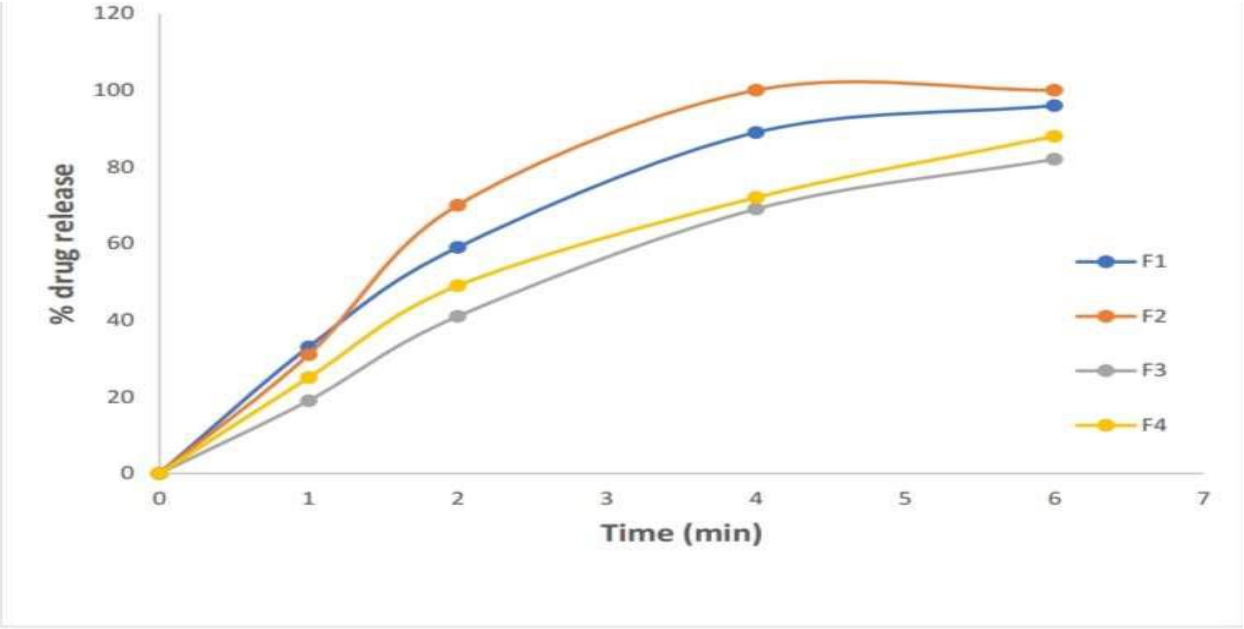

Figure 6: in vitro drug release from PVA

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