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FORMULATION AND EVALUATION OF DRUG RELEASE FROM CHLORHEXIDINE FILMS

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ABSTRACT

This study dealt with the release rate of chlorhexidine acetate from the various prepared films into citrate buffer (PH=5.03). The results revealed that, the release of chlorhexidine from films composed of different ratios of ethylcellulose (EC) and hydroxypropyl methylcellulose (HPMC) was different. As the ratio of HPMC increased the rate of drug release increased. In addition, films Composed of EC:HPMC in a ratio of 8:2 was found to be the most proper film, since about 35% of the drug was released over 8 hours. Incorporation of different concentrations of plasticizers (10, 20 and 30% w/w of polymer) showed an increase in the drug release with increasing plasticizer concentration. The effect of different plasticizers used can be arranged according to their effect on the rate of drug release from medicated films in the following descending order: polyethylene glycol 400>glycerin>propylene glycol. Morever, incorporation of different concentrations of enhancers (1% soduim dodecyl sulphate, urea (10 and 20%) and Tween 80 (5 and 10%) to the medicated selected films plasticzed with 20% propylene glycol enhanced drug release. Different concentrations of chlorhexidine acetate (3, 6, 9, 12 and 15% w/w of dry film) were tested. The results proved that the greatest drug release was observed from films containing 15% w/w of the drug. The effect of film thickness on the release rate was also tested using four different film thicknesses containing the same drug concentration. The results proved that, as the film thickness increased the percentage of drug release decreased. Finally, it was concluded that films composed of a mixture of EC and HPMC in a ratio of 8:2 plasticized with propylene glycol 20% and containing 10% Tween 80, produced about 85% chlorhexidine release after ten hours and was selected as the most suitable and proper formula for pharmaceutical applications.

INTRODUCTION

Topically antiseptic formulations containing chlorhexedine such as solution, cream and gauze dressing have been employed to treat wounds. However, due to the short duration of action, frequent applications are needed. Subsequently, great interest has developed regarding the use of medicated polymeric films in managing wounds. On this basis, it seemed advantageous to formulate a preparation in which antimicrobial agent is released from polymeric film over a prolonged period.

So, the purpose of this work is to formulate and evaluate polymeric films composed of mixture of EC and HPMC containing antimicrobial agent, chlorhexidine. Such film can be applied conveniently to the skin, releasing the drug in an effective concentration, thus its effect is produced for a reasonable time.

Chlorhexidine possess a high level of antibacterial activity , strong binding to the skin and very low toxicity (it does not causes systemic toxicity). It is employed for topical antiseptic application as skin disinfictant, wound irrigation , bladder irrigation, mouth washes, uretheral and vaginal irrigation(1).

Chlorhexidine is applied topically as cream 1% dusting powder 0.5%, gauze dressing 0.5%, dental gel 1% for gingivitis, antiseptic lozenges 1%, obestetric cream 1% during labour to prevent colonization and neonatal morbidity(2). Recently developed medicated aerosol- dressing of chlorhexidine with hemostatics(3).

EXPERIMENTAL

Materials :

Chlorhexidine diacetate (Sigma Chemical Co., St. Louis, Mo.,USA). Ethylcellulose 14cp. (BDH chemical ltd poole England). Propylene glycol, glycerin, polyethylene glycol 400, sodium citrate and citric acid (El-Nasr Co.Egypt). Polyethylene glycols 600, 1540, 4000 and 6000 Hoechest Chemikalian, Werk Gendort, Germany. Tween 80 (Merck, Schuchardt, Munchen, W. Germany). Urea, sodium dodecyl sulphate, methanol, methylene chloride (EL-Nasr Co. Egypt). All other reagents were of a highest grade available.

Preparation of polymeric medicated films :

Films of EC and HPMC were selected as the model system representing one typical approach of employing a hydrophilic polymer dispersed in a matrix of hydrophobic polymer . With this system, film varying in release pattern could be easily obtained by changing the proportions of EC and HPMC.

Films were prepared from polymer solution in a solvent of equal parts of casting solvent (methylene chloride : methanol). The solution contained 6% w/v of the polymer and specific weight of propylene glycol as a plasticizer which gave a film on a glass substrate that could be easily removed.

EC was added gradually, with continuous mixing by magnetic stirrer, to a 100 ml beaker containing the solvent, plasticizer or enhancer (if added) and the specific weight of chlorhexidine (5% w/w of dry film). HPMC was then added gradualy, with mixing, after all the EC had been dissolved. The beaker was covered with aluminium foil paper to prevent solvent evaportion. The solution was allowed to stand for about 30 minutes to remove entrapped air. Also air was removed from the polymer drug dispersion by ultrasonification for 5 minutes. The casting solution was transfered to a dust free cleaned and dried petri dish (area = 63.617cm^2) placed on a flat surface at room temperature . The petri dish

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was covered with an inverted glass funnel of stem orifice 0.6 cm in diameter. Clearance was provided for the escape of solvent vapours by raising the base of the funnel 2 cm just above the resting surface. The funnel was an aid in controlling the rate of evaporation of the solvent and reducing the blistering of the surface of the deposited film. The solvent was allowed to evaporate for 24 hours, the film was then removed from the petri dish to a desiccator containing anhydrous calcium chloride, where it was stored further 24 hours before use.

Several films were prepared to investigate the effect of polymeric modification ratios, plasticizer content, enhancer content, film thickness, drug loading on the release rate of chlorhexidine acetate from EC-HPMC films as follow:

1. Films of different ratios of EC:HPMC were prepared, as follows: 9:1, 8:2, 7:3, 6:4, 5:5, 4:6 , 3:7, 2:8 and 0:10, and plasticized with propylene glycol 10% w/w of polymer.
2. Non-medicated, medicated and plasticized EC-HPMC films in a ratio of 8:2 respectively were prepared. Plasticizers used were propylene glycol, glycerin and polyethylene glycol 400 in a concentration of 10, 20 and 30% w/w of polymer respectively.
3. Medicated plasticized EC-HPMC films (8:2), with different concentration of enhacers were prepared. Tween 80 (5 and 10 %), urea (10 and 20%) and sodium dodecyl sulphate (SDS) 1% were also used.
4. Medicated films containing 10% of different molecular weight polyethylene glycols namely 400, 600, 1540, 4000 and 6000.

Determination of release rate of chlorhexidine from films :

1. Rectangular films measuring 3cm x 4cm ($12cm^2$) were obtained by cutting a selected portion of cast film with a razor blade.
2. A thin coating of a suitable adhesive was applied to the slides (4cm x 6cm) which are used as a glass support, making sure that upper surface must be fitted to glass substrate and lower surface exposed to the medium.
3. The slide containing the film was placed at angle at the bottom of the vessel, the paddles of the instrument were allowed to rotate at 25 rpm which was the optimum speed to prevent rupturing of the film, and the distance between the film and paddle was constant in all experiments.
4. The vessels of the U.S.P dissolution tester were filled each with 100ml of citrate buffer (PH=5.03) to afford a sink condition.
5. To avoid buffer evaportion the vessels were kept covered except during sampling. Aliquots, each of 5ml sample were withdrawn at each time interval, and replaced by equivalent amounts of freshly prepared buffer, previously equilibrated at 37°C.
6. The run was continued for at least 8 hours or until the assays indicated that complete release has occured.
7. The amount of drug released from the films was determined spectrophotmetrically at 254nm in citrate buffer . Blank samples were obtained from release experiments of films containing the same components without drug.

RESULTS AND DISCUSSION

To study the release of chlorhexidine acetate, medicated films were fastend to a glass plate using thin layer of adhesive . Thus , the release of drug from the film was from one planner surface (lower surface).

First of all several trials were done for the proper selection of the best casting solvent and polymer concentration. It was found that the proper casting solvent for EC-HPMC was a mixture of methylene chloride and methanol in a ratio of 1:1 respectively. Also the best polymer concentration was fund to be 6% w/v.

The addition of HPMC improved, the overall properties of EC films, particularly with regard to brittleness . However the films were found to lose thir integrity at HPMC content greater than that contained in tested film (58% of polymer). This was quite apparent from the rapid passage of the drug accross the disintegrated films.

It was found that the release of chlorhexidine acetate was increased as the ratio of HPMC increased (Figure 1).

The complete release of drug (100%) from films composed of different ratios of EC:HPMC was as follows:

a) After one houre from 0:10, 1:9, 2:8 and 3:7 ratios.
b) After two houres from 4:6 ratio.
c) After three houres from 5:5 ratio.
d) After four houres from 6:4 ratio.

However, all these films were excluded due to rupturing during release studies, where they lose their integrity and as a result rapid release of drug occur. Ratio of 9:1 represented the most hydrophobic film and showed prolonged drug release, but they were excluded becuase of their brittleness and difficultly in removal completely from the glass substrate. Ratio of 8:2 also provided prolonged drug release where 35% of chlorhexidine acetate released over eight hours. Films formed of EC: HPMC at ratio of 8:2 were found to be the most suitable films due to its toughness, resiliency and resistant to rapid dissolution in aqueous medium.

The increase in the release of chlorhexidine acetate as the ratio of hydrophilic polymer increased can be attributed to the channels formed due to the presence of dispersed HPMC as channeling agent .

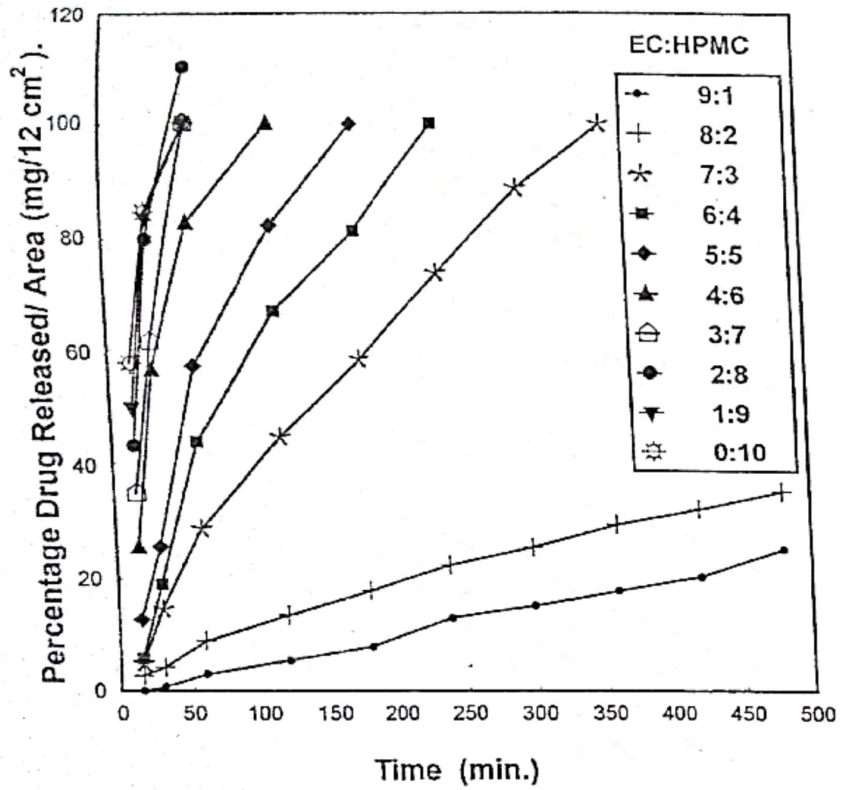

Fig.(1) : Percentage of chlorhexidine released from different ratios of EC-HPMC films

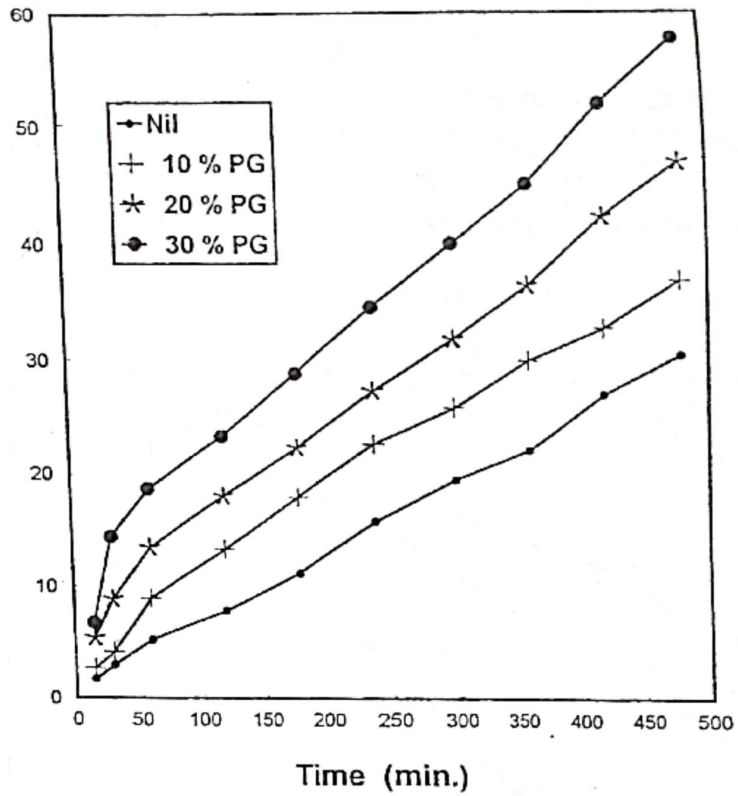

Fig.(2) : Percentage of chlorhexidine released from EC-HPMC films (8:2) unplasticized and plasticized with different concentrations of propylene glycol.

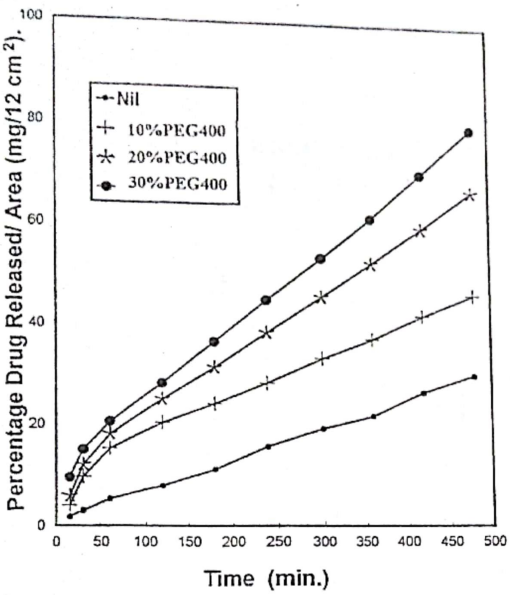

Fig.(3) : Percentage of chlorhexidine released from EC-HPMC films (8:2) unplasticized and plasticized with different concentrations of polyethylene glycol 400.

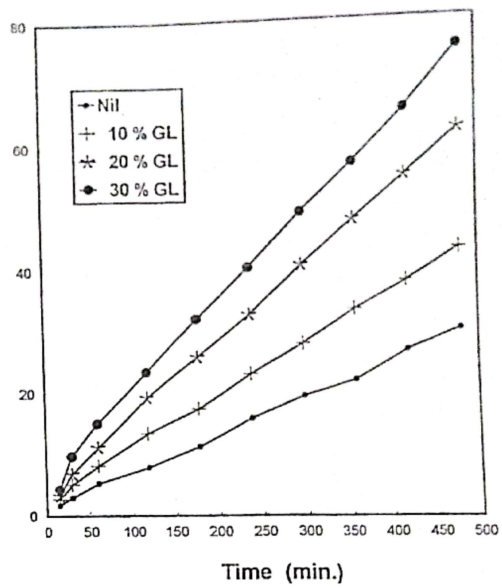

Fig.(4) : Percentage of chlorhexidine released from EC-HPMC films (8:2) unplasticized and plasticized with different concentrations of glycerin .

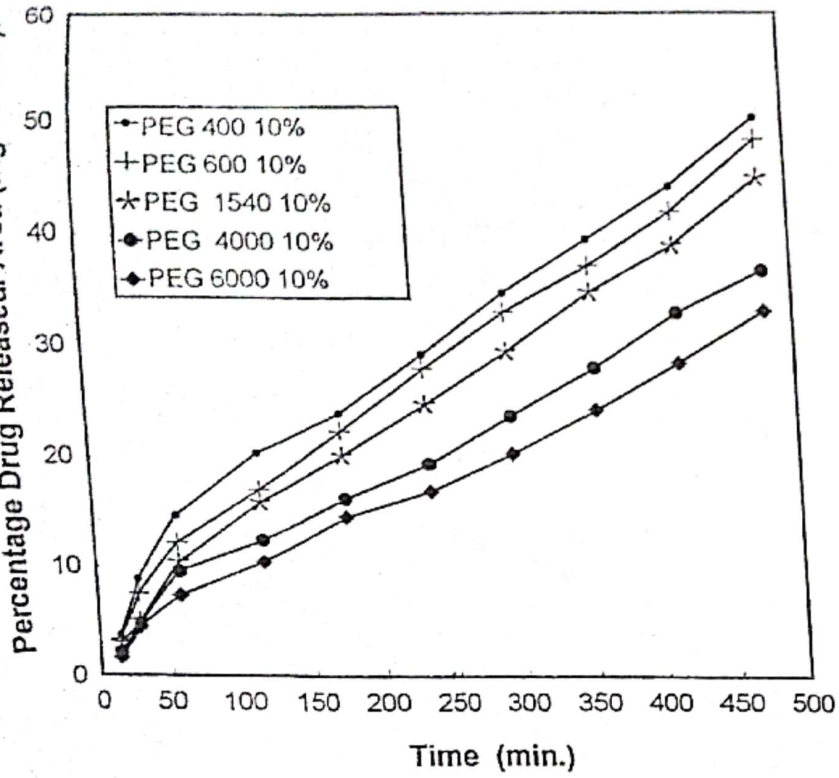

Fig.(5) : Percentage of chlorhexidine released from EC-HPMC films (8:2) plasticized with 10 % w/w of different molecular weights of polyethylene glycol .

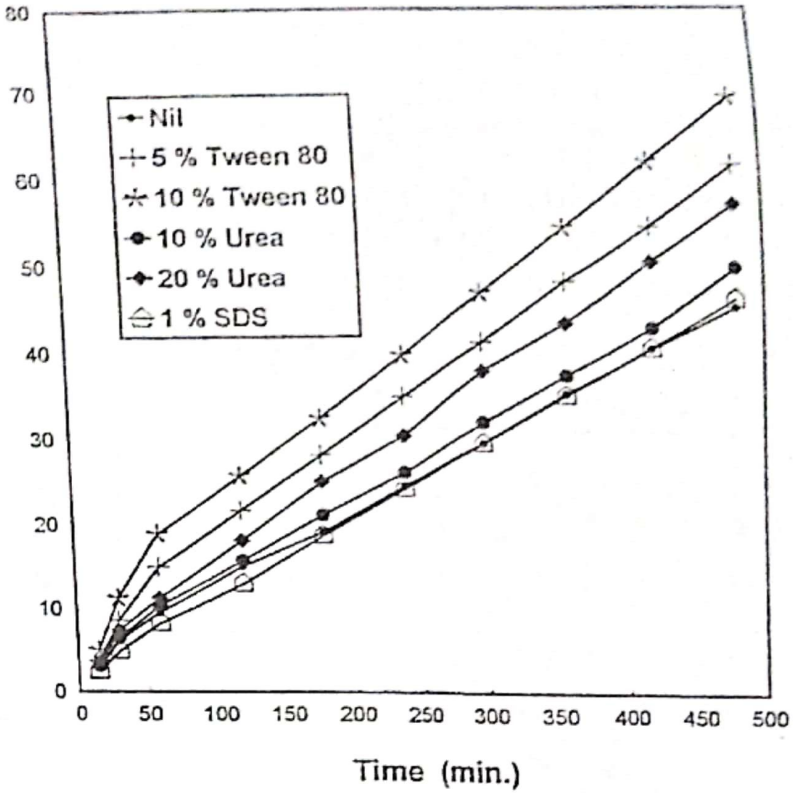

Fig.(6) : Percentage of chlorhexidine released from EC-HPMC films (8:2) plasticized with 20 % w/w of propylene glycol in the presense of different concentration of enhancers.

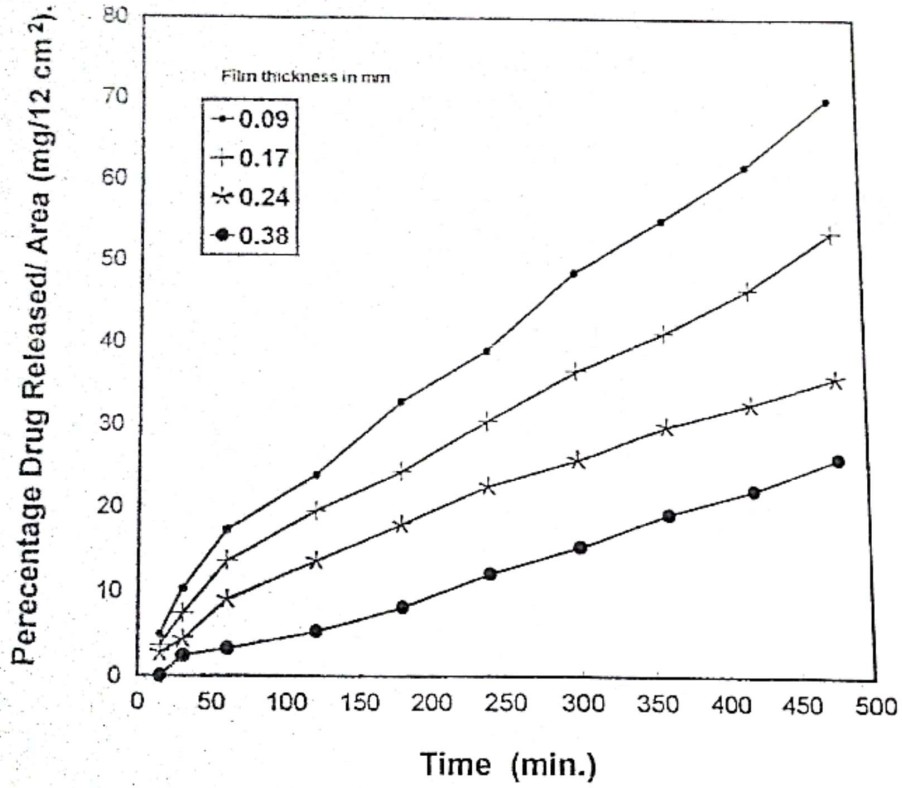

Fig.(7) : Percentage of chlorhexidine released from EC-HPMC films (8:2) plasticized with 10 % w/w of propylene glycol at different film thicknesses .

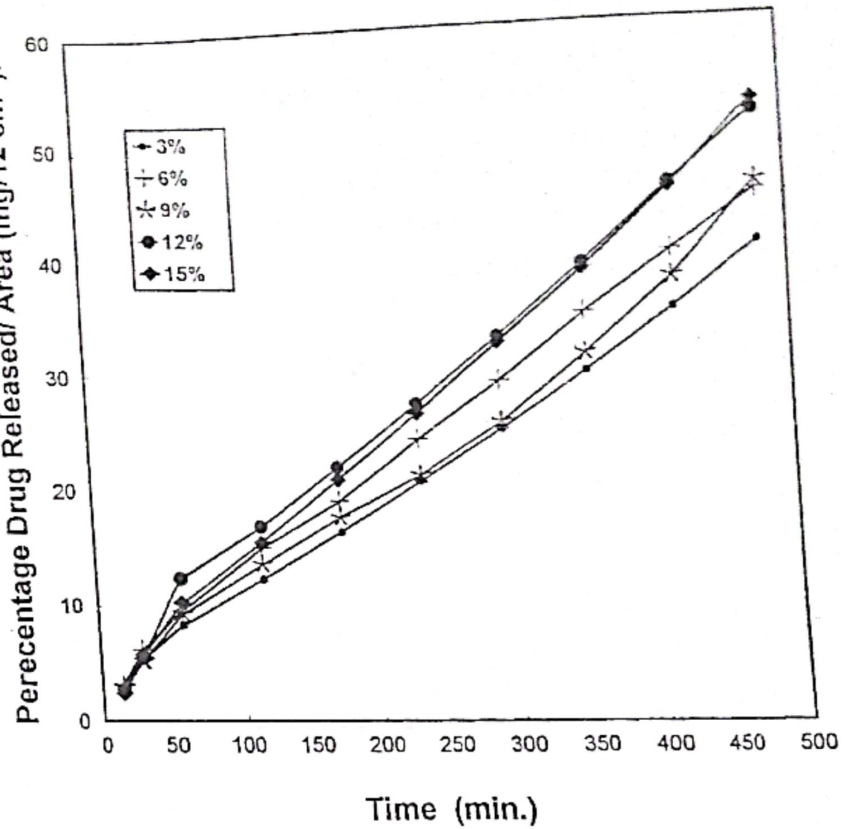

Fig.(8) : Percentage of chlorhexidine released from EC-HPMC films (8:2) plasticized with 20 % w/w of propylene glycol in the presence of different drug concentrations.

To the best film (EC:HPMC of 8:2 ratio), which was selected as mentioned above, different concentrations of plasticizers namely propylene glycol, glycerin and polyethlene glycol 400 (10, 20 and 30% w/w of polymer) were incorporated. The results (Figures 2-4) showed that as the concentration of plasticizers increased the percentage of drug release increased. In addition, the presence of polyethylene glycol 400 increased the rate of drug release with a relatively higher percentage than other plasticizers (glycerin and propylene glycol). This can be explained by leaching of PEG 400 from the prepared films with water resulted in the formation of large pores, which occupied by external solvent diffusing into the film. This suggestion was in a good agreement with those given by Samuelov et al.[4], Borodkin et al.[5], Safwat[6] and Gua[7,8].

The effect of different plasticizers used can be arranged according to their effect on the rate of drug release from medicated films in the following descending order: polyethylene glycol 400> glycerin>propylene glycol.

Incorporation of 10% polyethylene glycol of different molecular weights (400, 600, 1540, 4000 and 6000) to these films demonstrated that low molecular weights PEGs produced clear transparent films and higher drug release, while high molecular weights PEGs produced brittle white filmes which could not be removed completely from the petri dish and exhibited slow drug release. This phenomenon could be explained as follow: the plasticizing effeciency of the PEGs is decreased with increasing their molecular weights, and those with higher molecular weights exhibited phase separation. This suggestion was in agreement with those given by Sakellarious et al.[9].

The effect of different molecular weights of polyethylene glycol on the release of from polymeric films can be arranged in the following descending order: PEG 400 > PEG 600 > PEG 1540 > PEG 4000 > PEG 6000. These results were graphically illustrated in Figure 5.

The effect of different enhancres e.g. Tween 80, urea and sodium dodecyl sulphate (SDS) on chlorhexidine release rate was invetigated . It was found that the presence of these enhancers in the polymeric medicated films improved drug release. The corresponding concentrations of these enhancers were: 5 and 10% Tween 80, 10 and 20% urea and 1% SDS. The effect of different enhancers on the rate of chlorhexidine release can be arranged in the following descending order: Tween 80 > urea > SDS. The release of chlorhexidine from films containing the above mentioned enhancers was shown in Figure 6.

Results demonstrated that the best concentration which could signifcantly increase the release rate of chlorhexidine was 10% Tween 80, 20% urea and 1% SDS . Higher concentration of those enhancers led to a decrease in the rate of drug release . These reults were in a good agreement with that obtained by Mohamed A.I.[10], who mentioned that higher concentration of surfactants increases the number and diameter of micelles formation in which the drug molecules are trapped. Consequently a decreased rate of drug release is reflected. This study proved that Tween 80 was the most effecient enhancer, while SDS showed a minimal effect.

The effect of the film thikness on chlorhexidane release was also tested using four different film thicknesses namely 0.09, 0.17, 0.24 and 0.38mm containing the same drug concentration (13 mg/12 cm^2). The matrix was composed of mixture of EC-HPMC (8:2) plasticized with 10% propylene glycol. The results were graphically illustrated in Figure 7. This study showed that, as the film thickness increased the percentage of drug release decreased. The obtained results were in a good agreement with those observed by Samuelov et al.[4] Sellassie et al.[11].

The effect of drug concentration on the release rate constant was also studied using different concentrations of chlorhexidine acetate (3, 6, 9, 12 and 15% w/w of dry film) in EC-HPMC films (8:2) and plasticized with 20% propylene glycol. The obtained results were represnted in Figure 8 . The greatest drug release was observed from films containing 15% w/w of the drug. This is due to leaching of hydrophilic component (HPMC) which increase the external film area exposed to the solvent, and at the same time increases the internal porosity and decreases the tortuosity. The presence of drug in high concentration is considered another contribution of leaching out of drug. These results were in a good agreement with that observed for the release of chlorpheniramine and sodium salicylate from a hydropilic matrix[12,13].

Therefore, the proper formula was that of EC:HPMC in a ratio of 8:2, plasticized with 20% propylene glycol and containing 10% Tween 80. This flim composition represented the best formula because it has the above advantages that previously mentioned by Lim, et al.[14].

CONCLUSION

From the previously mentioned data, it can be concluded that:

1- The in-vitro evaluation of chlorhexidine release from ethlycellulose- hydroxypropyl methylcellulose film depends mainly on the modification of the polymeric ratio in the film, plasticizer content, enhancer content, film thickness and drug loading .

2- The most proper selected formula was found to be that composed of ethylcelluose and hydroxypropyl methylcellulose in a ratio of 8:2 .

3- The inclusion of polyol plasticizers in these films caused an increase in the amount of chlorhexidine acetate release depending on the concentration of plasticizer used . Polyethylene glycol gave the

highest release rate .

4- The inclusion of enhancers in these films increased the amount of chlorhexidine release depending on the concentration of enhancer used . Tween 80 gave the highest release rate and therefore film of EC : HPMC in a ratio of 8:2 plasticized with 20% propylene glycol in the presence of 10% Tween 80 represented the best formula, since 85% of drug was released over ten hours which is considered to be suitable and acceptable during handling.

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صياغه بعض الأغشية البوليمريه المحتويه على الكلور هيكسدين وتقييم درجة إنطلاق العقار منها

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تناول هذا البحث دراسه إنطلاق الكلورهيكسدين أسيتات من الأغشية المحضره إلى وسط محلول السترات المنظم أسه الأيدروچينى ٥،٣ . ودلت النتائج إنطلاق الكلورهيدكسدين من الأعشيه المكونه من نسب مختلفه من مادتى الإيثيل سيليلوز والأيدروكسى بروبيل ميثيل سيليوز كانت مختلفه بأختلاف تلك النسب وكلما زادت نسبة الأيدروكسى بروبيل ميثيل سيليلوز زادت درجة إنطلاق العقار . وبالإضافه إلى ذلك فلقد وجد أن الغشاء المكون من الأيثيل سيليلوز والإيدروكسى بروبيل ميثيل سيليلوز بنسبة ٨ : ٢ هو أفضل النسب حيث أن ٣٥٪ من العقار تم إنطلاقها خلال ٨ ساعات.

وكذلك فإن إضافة اللدائن إلى الغشاء (١٠ ، ٢٠ ، ٣٠٪) أدت إلى زيادة إنطلاق العقار وكلما زادت نسبة هذه اللدائن زادت نسبة إنطلاق العقار . وقد وجد أن مادة الأيثيلين چليكول ٤٠٠ تعطى أعلى معدل إنطلاق ثم تليها مادة الجلسرين ثم مادة البروبيلين چليكول . وبإضافة المواد المساعده (١٪ كبريتات دوديكل الصوديوم ، يوريا (١٠ ، ٢٠٪) وكذلك توين ٨٠ (٥، ١٠٪) إلى الغشاء وفى وجود ٢٠٪ من مادة البروبيلين چليكول كمادة لدنه وجد معدل إنطلاق العقار قد زاد . ولقد اختبرت تركيزات مختلفه من الكور هيكسدين أسيتات (٣،١ ٦ ، ٩ ، ١٢ وكذلك ١٥٪) وثبت أن أعلى درجة إنطلاق للعقار كانت فى نسبة ١٥٪ . وبالنسبة إلى سمك الغشاء فلقد وجد أنه كلما زاد سمك الغشاء كلما قل إنطلاق العقار .

ونستخلص من ذلك أن الغشاء المكون من الأيثيل سيليلوز والأيدروكسى بروبيل ميثيل سيليلوز بنسبه ٨ : ٢ مع إضافة ٢٠٪ من البروبيلين چليكول كمادة ملدنه وكذلك ١٠٪ توين ٨٠ تعطى إنطلاقا للدواء بنسبة ٨٠٪ بعد ١٠ ساعات ولذلك أختبرت كأنسب صيغه للتطبيقات الصيدلة .