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Design and Evaluation of Salbutamol Sulphate Transdermal Delivery System

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ABSTRACT

In the present study, transdermal formulations containing salbutamol sulphate (SS) using a hydroxypropyl methylcellulose (HPMC) as a hydrophilic matrix type films with different concentrations of plasticizers and enhancers such as polyethylene glycol-400 (PEG), propylene glycol (PG), glycerine (GL), and Tween-80 were prepared by solvent evaporation technique. All the prepared formulations were evaluated for their drug content, film thickness, *in vitro* release and *in vitro* permeation through rabbit skin into phosphate buffer pH 5.8. Results showed that the proper HPMC concentration of 4% w/v produced suitable film thickness and controlled drug release compared to the other tested concentrations. Also, HPMC matrices containing PEG and PG resulted in optimal controlled drug release within 6 hours where those matrices containing GL and Tween-80 showed the highest retardation of drug release. Therefore, the most satisfactory controlled release of SS was obtained from the matrices containing PEG and PG of 10 and 15% w/w of polymer. Also, their flexibility characteristics make them easier for removal from the glass substrate and more convenient for evaluation. Further *in vitro* permeation of SS from the selected HPMC films plasticized with PEG of 10, 15 and 20% w/w of polymer using rabbit skin as biological membrane was evaluated to give an idea of the drug permeation through the human skin. It was found that 44.76, and 78.43 percentages of SS were permeated after 6 hours, respectively.

INTRODUCTION

Transdermal drug delivery (TDD) is becoming an increasingly convenient and effective way to administer drugs. TDD has many advantages over other drug delivery routes. They provide constant blood level in the plasma for drug with a narrow therapeutic window, thus minimizing the risk of toxic side effects or lack of efficacy. Also they avoid first pass metabolism in the gastrointestinal tract and liver and allow drugs with poor oral bioavailability and/or short biological half lives to be administered at most, once a day, which can result in improved patient compliance [1-4].

The problem of gastrointestinal environment, such as chemical degradation of drug and gastric irritation, are avoided. Removing the transdermal drug reservoir, from stratum corneum can easily terminate drug input immediately ref.

Salbutamol sulphate is a Beta-2 agonist commonly used as a bronchodilator for the treatment of the chronic obstructive pulmonary disease. Salbutamol sulphate suffers from first pass metabolism, and as a result, about half of the administered dose is recovered in the urine as an active sulphate metabolite [5,6]. Several methods were attempted to formulate salbutamol sulphate controlled release preparations [7-9]. Thus, the designing of transdermal system is realised to exclude hepatic metabolism and to control the delivery of the drug to the blood circulation.

Salbutamol sulphate is significantly absorbed through the skin on topical application [10]. Therefore, the present study was an attempt to design salbutamol sulphate transdermally using hydrophilic polymer as a matrix forming transdermal film and to study *in vitro* drug release and permeation through rabbit skin. Also, kinetic studies of drug release from the different formulations were investigated.

MATERIALS AND METHODS

Materials

Salbutamol Sulphate, Shaphaco, (Yemen). Hydroxypropylmethyl-cellulose (50cps), (CID), (Egypt). Ethanol, Sigma Aldrich Chemie, Gumbo, (packed-Switzerland). Glycerine and propylene glycol (YDCO), Yemen. Polyethylene glycol (PEG, 400) Hoechest Chemikalian, Werk Gendort (Germany). Other chemicals and reagents were of analytical grades.

Adult male rabbits, weighing 2-2.5 kg.

Equipments

Ultraviolet Spectrophotometer Shimadzu UV-1610PC, (Japan). USP-dissolution tester Pharma test type PTW, (Germany). Constant temperature heating magnetic stirrer Thermally Co. (USA). Electronic balance Sartorius GmbH Göttingen, (Germany).

Methods:

I-Preparation of salbutamol sulphate transdermal films:

Hydroxypropylmethyl cellulose (HPMC) was selected as a matrix forming transdermal film representing one typical approach of employing a hydrophilic polymer with this system. Film release pattern could be easily obtained by changing the concentrations of HPMC, polyol plasticizers and/or enhancers. Transdermal films were prepared as follows: The accurate weight of HPMC (4% w/v) was added gradually to a mixture of ethanol and water (1:8.7) containing the plasticizer or enhancer (if added) and the specific weight of salbutamol sulphate (96 mg) was added to the solution with continuous mixing by a magnetic stirrer until complete dissolution.

The drug polymer solution was transferred to a clean dried glass Petri dish (area=28.27 cm^2) and placed on a flat surface at room temperature. The solvent was allowed to evaporate for 24 hours. The dried film was removed and a circular film of a 1.9 cm diameter (area =2.835 cm^2) was cut for *in vitro* evaluation [11-13].

Several transdermal films were prepared to investigate the effect of polymer concentrations, plasticizer concentrations or enhancer concentrations on film thickness and drug release rate of salbutamol sulphate from HPMC films as follow:

1- Preparation of medicated transdermal films with different concentrations of HPMC as 2, 3, 4, and 6% w/v plasticized with 10% w/w of polyethylene glycol-400.

2-Preparation of plasticized transdermal films using propylene glycol, polyethylene glycol-400, and glycerine in concentrations of 5, 10, 15, and 20% w/w of polymer which were added to medicated polymer solution containing 4% w/v of HPMC.

3-Preparation of transdermal films using Tween 80 as enhancer: Different concentrations of Tween-80 viz.: 1.5, 2.5, and 5%w/w of polyme were added to the medicated polymer solution containing 4% w/v of HPMC and 10%w/w of polyethylene glycol.

II- *In vitro* Evaluation of the prepared transdermal films:

1-Drug content:

Films of specified area of 2.835 cm^2 were cut and placed in 100 ml volumetric flask containing phosphate buffer pH 5.8. and stirred by magnetic stirrer for 2 hours. A blank was carried out using drug free films treated similarly. The solution was filtered and then analyzed spectrophotometrically at λmax 276 nm [13,14].

2-*In vitro* drug release from transdermal films:

In vitro release and skin permeation of salbutamol sulphate from the transdermal films were carried out using USP basket type dissolution apparatus as a diffusion cell in which the circular film of specified area of 2.835 cm^2 was attached to the outer closed part of the basket and covered with barriers, cellophane membrane or fresh rabbit skin which is fitted tightly. Fresh rabbit skin was excised from the chest of the rabbit and soaked in buffer solution for one hour.

The diffusion cell was immersed in the receptor containing 200ml phosphate buffer pH 5.8 and allowed to rotate at a speed of 50 rpm. The temperature was maintained at (37C' ±0.5). Aliquots of (5ml) were withdrawn from the receptor at regular predetermined intervals (0.25, 0.5,1,2,3,4,5, and 6, hours) and replaced with fresh medium from compensated cell. The drug content was analyzed spectrophotometerically. The cumulative percentage of salbutamole sulphate released was calculated and plotted against time for each film [13,15] All experiments were run in duplicate.

3-Kinetic study:

The mechanism of salbutamol sulphate release from matrices was determined by fitting the release profiles to various modelled, viz., zero order, and first order and Higuchi square root models. The coefficient of variation percentage was determined to select the model that yielded the best fit [16].

Table 1: *In vitro* release of salbutamol sulphate from matrices containing different concentrations of hydroxypropylmethyl cellulose and 10%w/w polyethylene glycol.

HPMC* Conc.	Percent of salbutamol sulphate released after the following time intervals (hrs)							
	1/4	1/2	1	2	3	4	5	6
2%	2.54	12.84	28.50	37.78	56.96	64.67	73.00	84.64
3%	00	5.40	26.85	33.62	48..91	57.43	64.07	69.70
4%	00	27.77	32.73	42.03	48.92	55.43	61.07	66.68
6%	2.88	2.78	13.58	25.96	34.70	40.05	45.04	49.61

*Hydroxypropylmethyl cellulose

Table 2: *In vitro* release of salbutamol sulphate from hydroxypropylmethyl cellulose matrices containing different concentrations of polyethylene glycol-400.

Conc. of PEG* (%w/w)	Percent of salbutamol sulphate released after the following time intervals (hrs)							
	0.25	0.5	1	2	3	4	5	6
Plain	10.76	12.43	19.15	25.27	33.54	37.56	43.20	48.25
5%	9.61	14.45	20.19	21.86	32.86	40.03	49.63	55.84
10%	00	27.77	32.73	42.03	48.92	57.43	62.07	66.68
15%	12.87	33.97	40.57	53.27	60.99	70.90	77.66	83.82
20%	00	5.10	20.28	38.33	54.36	69.90	82.87	95.45

*Polyethylene glycol-400

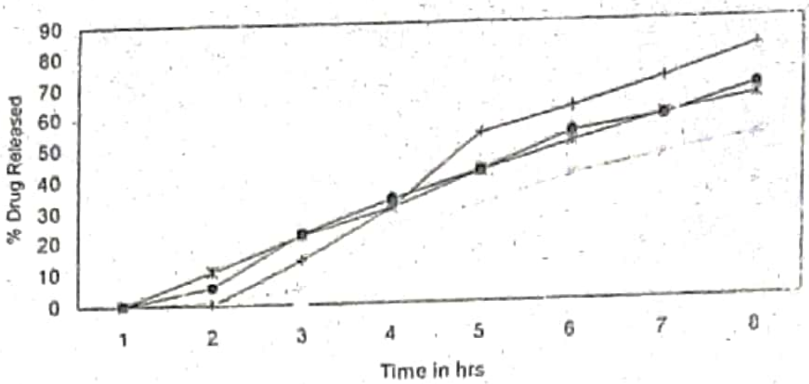

Fig 2 In-VitroReleased of salbutamol sulphate from HPMC Matrices containing Different Concentrations of Propylene glycol

Plain —— 5%w/w —x— 10%w/w —●— 15%w/w —+— 20%w/w

Table 3: *In vitro* release of salbutamol sulphate from hydroxypropylmethyl cellulose matrices containing different concentrations of propylene glycol.

Conc. of PG* (%w/w)	Percent of salbutamol sulphate released after the following time intervals (hrs)							
	0.25	0.5	1	2	3	4	5	6
Plain	10.76	12.43	19.15	25.27	33.51	37..56	43..20	48.25
5%	00	1.20	5.28	24.66	31.00	39.67	45.87	52.45
10%	00	10.89	21.67	30.32	41.55	50.78	58.82	64.88
15%	00	5.72	22.65	33.08	41.88	53.75	58.55	68.07
20%	00	00	13.80	30.51	53.91	62.09	70.6	81.11

*Propylene glycol

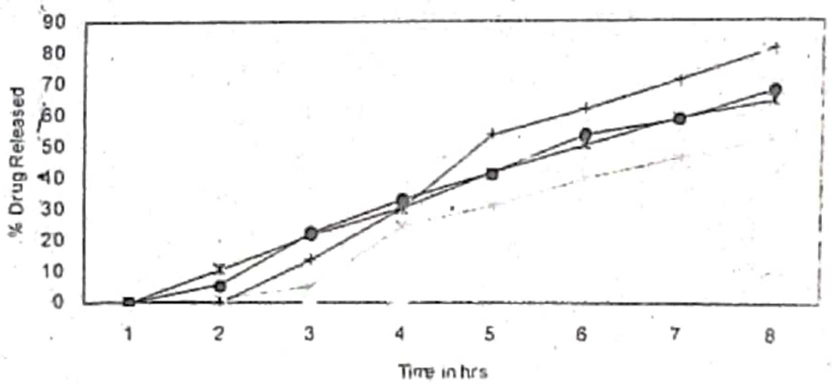

Fig 3: In-Vitro Release of salbutamol sulphate from HPMC Matrices Containing Different Concentrations of Propylene glycol

Plain —— 5%w/w —x— 10%w/w —●— 15%w/w —+— 20%w/w

Table 4: *In vitro* release of salbutamol sulphate from hydroxypropylmethyl cellulose matrices containing different concentrations of glycerin.

Conc. of GL* (%w/w)	Percent of salbutamol sulphate released after the following time intervals (hrs)							
	0.25	0.5	1	2	3	4	5	6
Plain	10.76	12.43	19.15	25.27	33.51	37.56	43.20	48.25
5%	00	5.92	18.90	20.55	24.34	32.67	38.45	44.35
10%	00	00	6.05	19.63	28.88	36.91	44.04	58.20
15%	00	5.54	12.80	23.10	30.98	42.85	54.80	62.60
20%	00	00	18.80	27.59	34.32	40.20	52.70	66.60

*Glycerine

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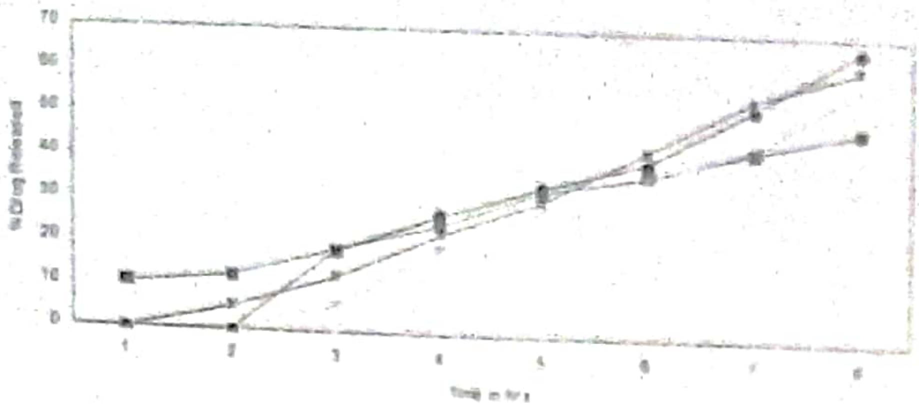

Fig 4: In-Vitro Release of Salbutamol Sulphate from HPMC Matrices Containing Different Concentrations of Glycerin

Table 5: *In vitro* release of salbutamol sulphate from hydroxypropyl methylcellulose matrices containing different concentrations of tween80

Tween80 Conc.	Percent of salbutamol sulphate released after the following time intervals (hrs):							
	0.25	0.5	1	2	3	4	5	6
Plain	10.76	12.43	19.15	25.27	33.51	37.56	43.20	48.25
1.5%	12.98	18.17	22.81	24.36	27.07	32.87	37.89	42.00
2.5%	.387	9.67	13.533	18.20	22.04	27.07	34.80	38.78
5%	21.67	38.67	46.01	50.27	59.93	61.87	66.13	72.67

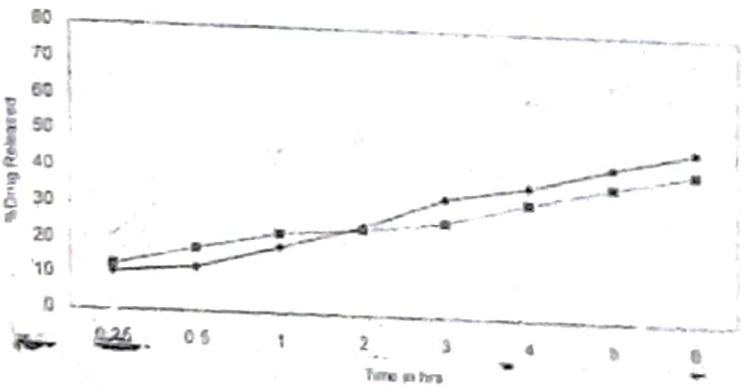

Fig 5: In-Vitro Release of Salbutamol Sulphate from HPMC Matrices Containing Different Concentrations of Tween80

Table 6: *In vitro* permeation of salbutamol sulphate from hydroxypropylmethyl cellulose matrices containing different concentrations of polyethylene glycol 400

Conc. of PEG (%w/w)	Percent of salbutamol sulphate released after the following time intervals (hrs)							
	0.25	0.5	1	2	3	4	5	6
10%	00	2.78	15.34	24.61	29.30	34.50	38.32	44.76
15%	5.22	14.5	21.72	29.90	37.04	41.70	49.66	56.65
20%	8.11	14.50	25.78	36.65	45.00	56.60	65.00	74.23

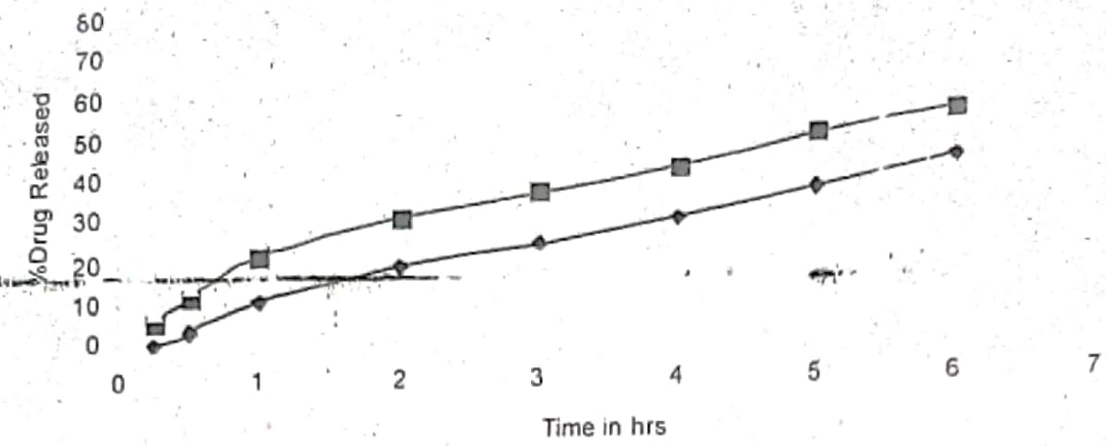

Fig.6 In-Vitro Permeation of Salbutamol Sulphate From HPMC Matrices Containing Different Concentrations of PEG

Table 7: Kinetics data of salbutamol sulphate release from HPMC matrices containing different concentrations of HPMCand 10% PEG.

HPMC Conc.	*C.V.%			Release order	K (h)$^{-1}$	$t_{1/2}$ (h)
	Zero order	First order	Diffusion controlled			
2%	14.04	2.57	5.96	First	0.293	2.37
3%	19.85	1.485	9.77	First	0.204	3.39
4%	4.11	0.440	4.58	First	0.139	4.95
6%	17.21	0.962	7.65	First	0.118	5.88

*C.V. %= Coefficient of variation percent

Table 8: Kinetics data of salbutamol sulphate release from HPMC matrices containing different concentrations of plasticizers.

Plasticizers	%(w/w) of polymer	*C.V.%			Release order	K (h)$^{-1}$	$t_{1/2}$ (h)
		Zero order	First order	Diffusion controlled			
Propylene glycol	Plain	6.89	0.359	4.05	First	0.094	7.45
	5%	15.98	0.717	11.37	First	0.133	5.22
	10%	14.45	0.818	5.48	First	0.173	3.99
	15%	16.59	1.14	6.81	First	0.187	3.69
	20%	15.79	1.66	10.324	First	0.286	2.42
Polyethylene glycol-400	5%	6.69	0.937	12.30	First	0.119	5.78
	10%	4.11	0.440	4.58	First	0.139	4.95
	15%	14.22	1.99	8.27	First	0.265	2.64
	20%	9.51	9.52	5.82	Diffusion	49.52	2.2
Glycerin	5%	18.31	1.02	13.72	First	.0918	7.54
	10%	8.56	1.15	16.22	First	0.143	4.84
	15%	6.27	1.05	11.8	First	0.165	4.19
	20%	16.67	2.04	15.55	First	0.171	4.05

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Table 9: Kinetics data of salbutamol sulphate permeated from HPMC matrices containing different concentrations of polyethylene glycol 400through rabbit skin.

PEG Conc.	*C.V.%			Release order	K (h)$^{-1}$	$t_{1/2}$(h)
	Zero order	First order	Diffusion controlled			
10%	20.27	1.063	9.84	First	0.0974	7.12
15%	11.54	0.842	6.18	First	0.123	5.63
20%	7.91	1.600	5.92	First	0.222	3.12

RESULTS & DISCUSSIONS

Selection of HPMC as a matrix forming transdermal film was done based on the primary studies of several polymers and the proper casting solvent for both drug and polymer, as smoothness of film and ease of removal from the glass substrate.

Formulation of transdermal films using hydroxy propyl methyl cellulose (HPMC), as a matrix and the incorporation of different polyol plasticizers were done. Also, drug content, film thickness, release profiles and kinetic study were evaluated.

Drug content uniformity test demonstrated that amount of salbutamol sulphate in each film of a circular area of 2.83 cm^2 was found to be uniform and contained 9 mg ±0.24 of salbutamol sulphate.*In vitro* release profiles of salbutamol sulphate from HPMC matrices are shown in tables 1-5 and figures 1-5. The effect of polymer concentrations on drug release and film thickness was studied. Table 1 and Fig.1 show that, the higher the polymer concentration the higher the retardation of drug release and the thicker the films . Thus, 84.64, 69, 70, 66.68 and 49.61 percent of salbutamol sulphate were released from films containing 2, 3, 4, and 6 %w/v of HPMC, respectively. These results were in agreement with those observed by Othman [11] and Ahmed [19].

The optimal film thickness and prolonged drug release were observed from the formula containing 4%w/v of HPMC. Therefore, transdermal films composed of 4% w/v of HPMC plasticized with 10%w/w of PEG-400, were considered the most suitable films due to their toughness, resiliency and ease of removal from the glass substrate. Incorporation of different concentrations of plasticizers namely, polyethylene glycol-400 (PEG-400), Propylene glycol (PG) and glycerine (GL), were carried out to the selected films to investigate their effects on drug release and elasticity of the films, Results were depicted in tables 2-4 and graphically illustrated in fig. 2-4. Thereby, the dissolution profile of salbutamol sulphate from HPMC matrices plasticized with different concentrations of polyethylene glycol-400 (PEG-400) namely 5, 10, 15 and 20 % w/w of polymer, showed that, the higher the concentration of PEG 400 the higher the retardation of drug release and the elasticity of the films. On the other hand, optimal controlled drug release and enough flexibility were noted from a HPMC matrices containing 5 and 10% PEG as well as 55.84 and 66.68 percent released after 6 hours respectively. Also, as the concentration of PG increased the percentage of drug release and flexibility were increased. However, the higher retardation of drug release was observed from those films plasticized with 5 and 10% PG where 52.45 and 64.88 percent of drug, respectively were released after 6 hours. While 68.07 and 81.11 percent of drug released from matrices containing 15 and 20% PG, respectively. The presence of 5, 10, 15 and 20 % GL exhibited higher retardation of drug release but insufficient flexibility compared to the previous plasticized films. It was cleared that to plasticizers, PEG 400 and PG, showed more acceptable controlled release and flexibility compared to those plasticized with Glycerine, Also the increase of drug release compared to the unplasticized films can be explained by leaching of plasticizers from plasticized films with water resulting in formation of pores, which allow ease of passage of drug molecules. This suggestion was in agreement with what was given by several authors [11,17,18]Addition of different concentrations of Tween 80, as enhancers, 1.5, 2.5, and 5% (w/w of polymer), was studied. It could be found from table 5 and fig 5 that, the higher the concentration of Tween 80 the higher the drug release. Thus, HPMC film containing 5% Tween 80 exhibited higher drug release, where those containing low concentrations (1.5 and 2.5%) have no enhancing effect.Regarding the selection of the best films (matrix) to be used for further evaluation, HPMC films plasticized with PEG and PG are more flexible, transparent and smooth compared to HPMC films plasticized with GL. Also, HPMC films prepared with different concentrations of Tween 80 are opaque, brittle and can't be easily removed from the glass substrate.The skin permeation of salbutamol sulphate from the selected transdermal films plasticized with 10, 15 and 20 % PEG are illustrated in table 6 and fig 6. It was found that, the amount of drug permeated was increased as the concentration of PEG increased. Hence, HPMC films containing 10 and 15% PEG showed more controlled drug release compared to that observed from film plasticized with 20% PEG, where 44.76, 56.55 and 74.43 percent were permeated, respectively. Therefore, the permeation of drug through the skin of rabbit was lower compared to that permeated through artificial membrane. This variation was due to the large pore size of the artificial membrane compared to that of the skin [20]. Results indicated that transport of drug across the skin suggests the prediction of the permeation of SS through human skin that can be used for treatment of chronic asthmatic patients.

Mechanism of drug release The release rate of salbutamol sulphate from HPMC films or matrices was determined by fitting the release profiles in various kinetic models viz., zero order, first order and diffusion controlled mechanism. The least coefficient of variation percent (% CV) was determined to select the model, which yields the best fit. The release rate constants of salbutamol sulphate from HPMC films exhibited first order model process. It was clearly noticed that, the release rate constants were increased with increasing plasticizer concentrations. On the other hand, longer half-life of drug release was observed for HPMC films containing lower concentrations of plasticizers. Results were depicted in tables 7-9

CONCLUSION

From the previously mentioned data, It can be concluded that. the *in vitro* evaluation of salbutamol sulphate from HPMC film depends mainly on polymeric concentrations. plasticizers and enhancer content. The selected formula was found to be that composed of HPMC 4% w/v. Also, smooth, flexible and transparent films plasticized with PEG where PG was observed???? compared to hard and rough films plasticized with the glycerine or opaque and brittle films containing Tween 80 as enhancer.The best transdermal films plasticized with 10, 15 and 20% polyethylene glycol were selected for further *in vitro* evaluation using rabbit skin as a membrane. An optimal controlled drug release within 6 hours was attained.

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تصميم وتقييم كبريتات السالبيتمول في نظم إيصال دوائي عبر الجلد

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تم عمل صياغات متعددة في صورة أغشية كأنظمة إيصال سطحية محتوية على عقار كبريتات السالبيوتامول باستخدام هيدروكسي بروبيل مثيل السليلوز كمادة غشائية محبة للماء ، ما استخدمت تركيزات مختلفة من الملدنات والمحفزات متمثلة في جليكول 400 عدد الايثيلين وبروبيلين الجليكول والجلسرول وعديد السوربات 80. وقد تحضير هذه الصياغات باستخدام تقنية التبخير.