Bull. Pharm. Sci., Assiut University, Vol. 35, Part 1, 2012, pp. 83-95.

CONTROLLED RELEASE TABLET FORMULATIONS OF ISOXSUPRINE HYDROCHLORIDE USING DIRECT COMPRESSION TECHNIQUE

Ahmed A. Aboutaleb, Sayed I. Abdel- Rahman* and Jelan A. Abdel-Aleem

Department of Industrial Pharmacy, Faculty of Pharmacy, Assiut University, Assiut 71524, Egypt

يعتبر عقار هيدروكلوريد الايزوكسوبرين موسعا للأوعية الدموية الطرفية. تم تحضير العقار فى صورة أقراص ممتدة المفعول من أجل زيادة درجة إتباع المريض لتعليمات تعاطي الدواء عن طريق تقليل عدد مرات تناول الجرعات وكذلك الحد من التأثيرات الجانبية للعقار. وذلك باستخدام نسب مختلفة من المواد عديدة الجزيئات القابلة والغير قابلة للذوبان فى الماء إما بمفردها أو على هيئة مخاليط. تمت دراسة تأثير استخدام أنواع وتركيزات مختلفة من المواد عديدة الجزيئات على معدل وديناميكية الإتاحة لهيدروكلوريد الايزوكسوبرين من الأقراص المختبرة باستخدام طريقة الأس الهيدروجيني المتغير. وجد أن زيادة تركيز المواد عديدة الجزيئات المستخدمة من (3.34 إلى 30% نسبة وزنية) أدى إلى تأخير معدل الإتاحة للعقار من الأقراص. ولقد وجد أن الأقراص المحتوية على العقار وهيدروكسى بروبيل ميثيل السيليلوز 15000 او إيدراجيت RSPM بنسبة وزنية 30% أعطت أفضل فاعلية فى إتاحة العقار على المدى الطويل. كما وجد أن الأقراص المحتوية على العقار (10% نسبة وزنية) ومخلوط هيدروكسى بروبيل ميثيل السيليلوز (10% بنسبة وزنية) وإيدراجيت RSPM (40% نسبة وزنية) وكذلك الأقراص المحتوية على العقار (10% نسبة وزنية) ومخلوط وإيدراجيت RSPM (10% نسبة وزنية) وإيدراجيت RLPO (40% نسبة وزنية) أعطت أفضل معدل انطلاق طويل المدى للعقار مقارنة بالأقراص الأخرى. تتبع ديناميكية إتاحة هيدروكلوريد الايزوكسوبرين من الأقراص المحتوية على بوليمر واحد معادلة هيجوشى للانتشار بينما وجد أن إتاحة العقار من بعض الأقراص ممتدة المفعول المحتوية على مخاليط البوليمرات تتبع معادلة الرتبة صفر.

Isoxsuprine hydrochloride is a peripheral vasodilator. It is advisable to prepare the drug in sustained release dosage forms to improve patient compliance and to achieve a steady state blood level with minimum side effects. Different hydrophilic and hydrophobic polymers in addition to their combinations were used in different ratios to select the best level of the matrix forming material that provides the most sustaining effect. The effect of different types and concentrations of polymers on the release rate of the drug was investigated. The drug release decreased by increasing the concentration of the polymer in all the studied formulations. Tablet formula containing either 30% (w/w) HPMC 15000 or 30% (w/w) Eudragit RSPM gave the most sustaining effect among the single polymers. The drug release rate from tablets prepared using polymer blends is slower compared to that from those containing single polymers. The slowest drug release was obtained from tablet formulae containing: drug, 10% (w/w) HPMC 15000 and 40% (w/w) Eudragit RSPM and drug, 10% (w/w) Eudragit RSPM and 40% (w/w) Eudragit RLPO. The release of isoxsuprine HCl from matrices prepared using single polymer followed Higuchi's diffusion model. However, zero-*order release kinetics was elucidated for the release of isoxsuprine HCl from the investigated polymer blends in phosphate buffer (pH 6.8).*

INTRODUCTION

Pharmaceutical methods for extending drug action involve the design of the dosage form in such a way that it affects the release rate of the drug without affecting its chemical or biological characteristics. Among the methods used to formulate oral extended release products is retardation of drug release by the use of polymeric materials[1]. Polymers are uniquely suited as materials of construction for oral delivery systems. The polymers offer a wide range of properties such as diffusivity, permeability, and solubility that are important

Received in 7/7/2012 & Accepted in 2/8/2012

*Corresponding author: Sayed I. Abdel- Rahman, E-mail: boudysayed@yahoo.com

to achieve controlled delivery. These polymers have been broadly grouped into water-soluble polymers (hydrophilic polymers) and water-insoluble polymers (hydrophobic polymers)[2]. The increasing need for suitable polymers to achieve a desired drug release has facilitated screening of a large variety of both synthetic and natural polymers for their ability to retard the release of specific drug substances. Since the cost of synthesizing a new polymeric substance and testing for its safety is costly and tedious, a new focus has been directed towards investigating the use of polymer blends of pharmaceutically approved polymeric materials as matrix excipients to retard drug release[3]. However, these systems are more complex than coatings based on only one polymer and care has to be taken when using this type of formulations. The use of polymer blends as coating materials for controlled drug delivery systems can offer major advantages, including: (i) facilitated adjustment of desired drug release patterns, mechanical properties and drug release mechanism[4], (ii) improved film formation and storage stability[5], and (iii) the possibility to develop novel strategies for site specific drug delivery within the gastrointestinal tract[6]. Hence, isoxsuprine HCl sustained release tablets were formulated using different hydrophilic polymers namely; methyl cellulose (MC), sodium carboxymethyl cellulose (NaCMC) and hydroxypropyl methyl cellulose 15000 (HPMC 15000) in addition to hydrophobic polymers; ethyl cellulose (EC) and methacrylate copolymers; Eudragits RS100, RL100, RLPO and RSPM either single or in combinations. The prepared tablet formulations were tested for their drug content uniformity, weight uniformity, tablet diameter, tablet thickness, friability and hardness. The release of the drug from the prepared tablets was also studied. The *in-vitro* release profiles of isoxsuprine HCl from the prepared tablets were constructed and analyzed to determine the release kinetics of the drug from the formulations.

MATERIALS AND METHODS

Materials

- Isoxsuprine HCl was kindly supplied by SEDECO Company, Cairo, Egypt.
- Ethyl cellulose (EC), Hydroxypropyl methyl cellulose 15000 (HPMC 15000), Methyl cellulose (MC), and Sodium carboxymethyl cellulose (NaCMC), were supplied from Aldrich Chemicals Co., USA.
- Eudragit RL100, Eudragit RS100, Eudragit RLPO, and Eudragit RSPM, were supplied from Röhm Pharma, Darmstadt, Germany.
- Anhydrous lactose was supplied from Shefield Chemical, N.J. USA.
- Microcrystalline cellulose (Avicel pH 101) was obtained from FMC O., Ireland.
- Magnesium stearate was obtained from El-Nasr Pharmaceutical Chemicals Co., Egypt.
- All other chemicals and solvents were of analytical grade, and were used as received.

Equipment

- Single punch Tablet Machine, Korsch-Berlin, Ek/0, Frankfort, Germany- Erweka tablet hardness tester, type TAB, G.m.b.H., Germany.
- Erweka friabilator apparatus, G.m.b.H., Germany.
- Micrometer, Mitutoyo Corporation, Japan.
- Electric sensitive balance (Precisa 205 A, Switzerland).
- UV-visible Spectrophotometer, JENWAY-Model 6305, England.
- pH meter, JENWAY-Model 3310, England.
- Dissolution Apparatus, SR6 Dissolution Test Station, Hanson Research Corporation, Chatsworth, California, USA.

Methods

Preparation of isoxsuprine HCl sustained release tablets

Isoxsuprine HCl sustained release tablets were prepared by mixing isoxsuprine HCl (20 mg/tablet) with the different studied polymers either single or in combinations in different weight ratios and the other additives. Single polymers were added in the following weight ratios, 3:1, 2:1, 3:2, 1:1, 1:2 and 1:3, drug : polymer and these polymer ratios represent the following percentage from the tablet weight 3.34%, 5.00%, 6.67%, 10.00%, 20.00% and 30.00% respectively. In case of polymer combinations, four weight ratios were used 1:1:1, 1:1:2, 1:1:3 and 1:1:4, drug : polymer 1 : polymer 2, respectively. Diluent was added and mixing was performed using the serial mixing procedure in a mortar for at least five minutes

for each step. This was followed by tumbling mixing in a clean glass bottle for about fifteen minutes. Magnesium stearate was then added to the blend and mixed for another five minutes. The produced mixtures were compressed into tablets using single punch tablet machine equipped with a flat faced 8 mm punch. The machine was adjusted to produce tablets weighing 200 mg.

Tables 1-4, show the composition of the prepared isoxsuprine HCl sustained release tablet formulations and the amount of each ingredient in milligram (mg). Isoxsuprine HCl sustained release tablet formulations prepared using hydrophilic polymers are given the symbols (D1-D19). The prepared isoxsuprine HCl sustained release tablet formulations containing hydrophobic polymers are given the symbols (D20-D49). The symbols (D50-D69) are given to the tablets prepared using polymer blends.

The prepared isoxsuprine HCl sustained release tablets were evaluated for the following parameters[7]: tablet weight uniformity, drug content uniformity, tablet friability, tablet diameter, tablet thickness and tablet hardness.

***In-vitro* release of isoxsuprine HCl from the prepared sustained release tablets**

The USP dissolution apparatus II (paddle-type) rotating at 100 rpm was utilized. The dissolution medium was 500 ml of dilute HCl (pH 1.2) for the first 2 hrs, after which the pH of the dissolution medium was increased to pH 6.8 by adding tribasic sodium phosphate powder[8]. The dissolution medium was previously degassed and warmed to 37±0.5°C. At the specified time intervals, samples of 5 ml were withdrawn from the dissolution medium using volumetric pipette with cotton plug at its tip and replaced immediately with the same volume of the fresh dissolution medium maintained at the same temperature. The amount of isoxsuprine HCl was determined spectrophotometrically at λ_{max} 275 nm, using the same dissolution medium as a blank. All assays were done in triplicates and the mean value and standard deviation (SD) were calculated.

Table 1: Composition of 20 mg isoxsuprine HCl tablets prepared by direct compression technique using hydrophilic polymers.

Formula No	Amount of ingredient used in each tablet formula (mg)				
	MC	NaCMC	HPMC 15000	Avicel pH101	Anhydrous lactose
D1	-	-	-	94.00	94.00
D2	6.67	-	-	85.67	85.67
D3	10.00	-	-	84.00	84.00
D4	13.33	-	-	82.34	82.34
D5	20.00	-	-	79.00	79.00
D6	40.00	-	-	69.00	69.00
D7	60.00	-	-	59.00	59.00
D8	-	6.67	-	85.67	85.67
D9	-	10.00	-	84.00	84.00
D10	-	13.33	-	82.34	82.34
D11	-	20.00	-	79.00	79.00
D12	-	40.00	-	69.00	69.00
D13	-	60.00	-	59.00	59.00
D14	-	-	6.67	85.67	85.67
D15	-	-	10.00	84.00	84.00
D16	-	-	13.33	82.34	82.34
D17	-	-	20.00	79.00	79.00
D18	-	-	40.00	69.00	69.00
D19	-	-	60.00	59.00	59.00

For all formulae: total tablet weight was 200 mg and magnesium stearate 1% of total tablet weight was used as a lubricant.

Table 2: Composition of 20 mg isoxsuprine HCl tablets prepared by direct compression technique using ethyl cellulose and Eudragit RL100.

Formula No	Amount of ingredient used in each tablet formula (mg)			
	Ethyl cellulose	Eudragit RL100	Avicel pH101	Anhydrous lactose
D20	6.67	-	85.67	85.67
D21	10.00	-	84.00	84.00
D22	13.33	-	82.34	82.34
D23	20.00	-	79.00	79.00
D24	40.00	-	69.00	69.00
D25	60.00	-	59.00	59.00
D26	-	6.67	85.67	85.67
D27	-	10.00	84.00	84.00
D28	-	13.33	82.34	82.34
D29	-	20.00	79.00	79.00
D30	-	40.00	69.00	69.00
D31	-	60.00	59.00	59.00

For all formulae: total tablet weight was 200 mg and magnesium stearate 1% of total tablet weight was used as a lubricant.

Table 3: Composition of 20 mg isoxsuprine HCl tablets prepared by direct compression technique using different Eudragits.

Formula No.	Amount of ingredient used in each tablet formula (mg)				
	Eudragit RS100	Eudragit RSPM	Eudragit RLPO	Avicel pH 101	Anhydrous lactose
D32	6.67	-	-	85.67	85.67
D33	10.00	-	-	84.00	84.00
D34	13.33	-	-	82.34	82.34
D35	20.00	-	-	79.00	79.00
D36	40.00	-	-	69.00	69.00
D37	60.00	-	-	59.00	59.00
D38	-	6.67	-	85.67	85.67
D39	-	10.00	-	84.00	84.00
D40	-	13.33	-	82.34	82.34
D41	-	20.00	-	79.00	79.00
D42	-	40.00	-	69.00	69.00
D43	-	60.00	-	59.00	59.00
D44	-	-	6.67	85.67	85.67
D45	-	-	10.00	84.00	84.00
D46	-	-	13.33	82.34	82.34
D47	-	-	20.00	79.00	79.00
D48	-	-	40.00	69.00	69.00
D49	-	-	60.00	59.00	59.00

For all formulae: total tablet weight was 200 mg and magnesium stearate 1% of total tablet weight was used as a lubricant.

Table 4: Composition of 20 mg isoxsuprine HCl tablets using polymer blends.

Formula No.	Amount of ingredient used in each tablet formula (mg)						
	HMPC 15000	Na CMC	EC	Eudragit RLPO	Eudragit RSPM	Avicel PH101	Anhydrous lactose
D50	20	20	-	-	-	69	69
D51	20	40	-	-	-	59	59
D52	20	60	-	-	-	49	49
D53	20	80	-	-	-	39	39
D54	20	-	20	-	-	69	69
D55	20	-	40	-	-	59	59
D56	20	-	60	-	-	49	49
D57	20	-	80	-	-	39	39
D58	20	-	-	-	20	69	69
D59	20	-	-	-	40	59	59
D60	20	-	-	-	60	49	49
D61	20	-	-	-	80	39	39
D62	-	-	20	-	20	69	69
D63	-	-	40	-	20	59	59
D64	-	-	60	-	20	49	49
D65	-	-	80	-	20	39	39
D66	-	-	-	20	20	69	69
D67	-	-	-	40	20	59	59
D68	-	-	-	60	20	49	49
D69	-	-	-	80	20	39	39

For all formulae: total tablet weight was 200 mg and magnesium stearate 1% of total tablet weight was used as a lubricant.

Kinetic analysis of the drug release from the prepared sustained release tablets

The kinetic parameters for the *in-vitro* release of isoxsuprine HCl from the prepared sustained release tablets were determined and analyzed in order to explain the mechanism of the drug release. The kinetic data were plotted by linear regression according to zero and first-order kinetics as well as simplified Higuchi model.

RESULTS AND DISCUSSION

Standard calibration curves of isoxsuprine HCl in 0.1 N HCl solution of pH 1.2 and phosphate buffer of pH 6.8 were found to obey Lambert-Beer's law within the concentration range (2-20 µg/ml). Isoxsuprine HCl sustained release tablets prepared using different polymers were uniform in weight and tablet weights of all the studied formulations were found to be within the Pharmacopeial limits. Isoxsuprine HCl sustained release tablets were uniform in thickness and diameter. The values of friability (% loss) were ranged from 0.364 to 0.611%, which are acceptable values as the % loss must not be more than 1%. The hardness values of tablets were within the range of 4.5-7.1 kg which is also accepted range of hardness variation[9].

***In-vitro* release of isoxsuprine HCl from the prepared sustained release tablets**

Figures 1-3 show the efect of different ratios of the investigated hydrophilic polymers on isoxsuprine HCl release from the prepared tablets using pH-shift method.

Figure 1 shows the release profiles of isoxsuprine HCl from the prepared tablets containing different ratios of MC. The release of isoxsuprine HCl from tablets containing the drug alone (Formula D1) is rapid and complete drug release is obtained after 45 min. The incorporation of MC in isoxsuprine HCl tablets with different ratios (Formula D2-D7) resulted in a decrease in the release rate of isoxsuprine

HCl from these tablets than that from tablets containing the drug alone (Formula D1). This sustaining in the drug release may be attributed to the presence of MC, which is a non-ionic swelling hydrophilic polymer. The process of release of the drug from the hydrophilic polymer-drug matrix involves water penetration into the dry matrix, hydration and gel formation of this polymer followed by the diffusion of the dissolved drug in the gel[9]. As shown in figure 1, the release rate of isoxsuprine HCl was slowed upon increasing the concentration of MC from 3.34 to 30% (w/w). About 88% of the drug was released from the tablets containing 3.35% (w/w) MC, formula D2, after 90 min., while the tablets containing 30% (w/w) MC, formula D7 released about 69% of the drug after the same time. This decrease in the drug release rate may be due to the increase in the thickness of the gel layer upon increasing the concentration of the polymer in the tablets.

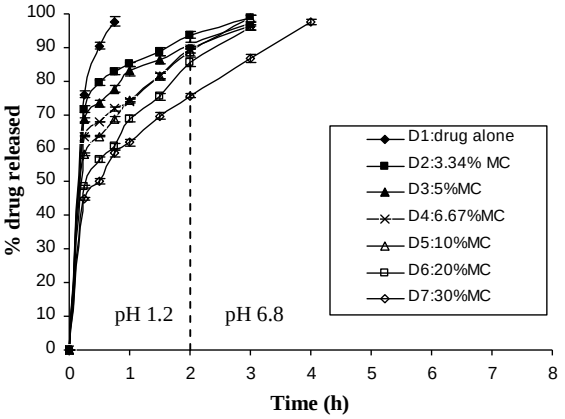

Fig. 1: Release profiles of isoxsuprine HCl from tablets containing different ratios of methyl cellulose.

Figure 2 shows the release profiles of isoxsuprine HCl from tablets prepared using different ratios of NaCMC. It is clear that the drug release rate decreased as the percent of NaCMC in the matrix is increased. The presence of 30% (w/w) NaCMC in the tablet (formula D13) sustained the release of isoxsuprine HCl to 5 hrs. This sustaining effect of the drug release can be attributed to the presence of NaCMC, which is swellable cellulose ether. Upon hydration, tablets containing NaCMC, behaved as a gel-like system, thereby creating a gelatinous barrier through which the drug diffuses during the dissolution process. The formation of such a gel layer around the drug particles might account for the retardation of the drug release from the prepared tablets[10]. Similar behaviour was observed with matrix tablets containing diltiazem HCl and NaCMC[11].

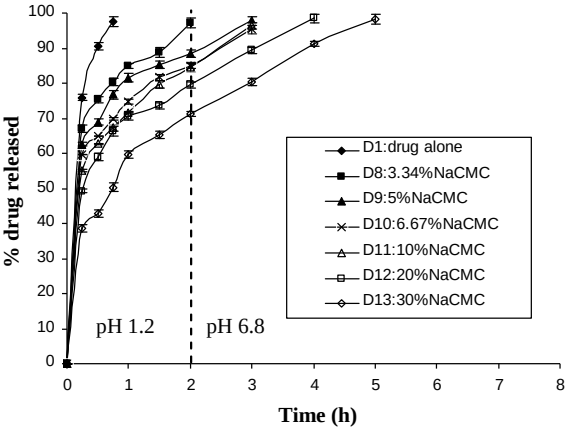

Fig. 2: Release profiles of isoxsuprine HCl from tablets containing different ratios of sodium carboxymethyl cellulose.

Figure 3 represents the drug release profiles of isoxsuprine HCl from tablets containing different ratios of HPMC 15000. The release of isoxsuprine HCl markedly decreased with increasing HPMC 15000 concentration. An increase in HPMC concentration resulted in an increase in the viscosity of the gel layer as well as the formation of a gel layer with a longer diffusional path, decreasing the drug release[12]. Similar results were obtained with tablets prepared from diclofenac sodium and HPMC[13].

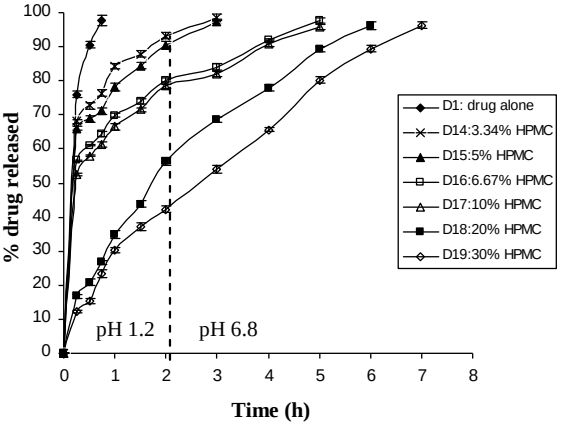

Fig. 3: Release profiles of isoxsuprine HCl from tablets containing different ratios of HPMC 15000.

Figure 4 shows the release profiles of isoxsuprine HCl from tablets containing 30% (w/w) of different hydrophilic polymers. As shown from this figure, HPMC 15000 (formula D19) shows the most sustaining effect (complete drug release was obtained after 7 hrs) when used in the attributed to its nature as a highly swellable non-ionic hydrophilic polymer. The sustaining effect of the three tested hydrophilic polymers on drug release was found to be in the following descending order: HPMC 15000 > NaCMC > MC.

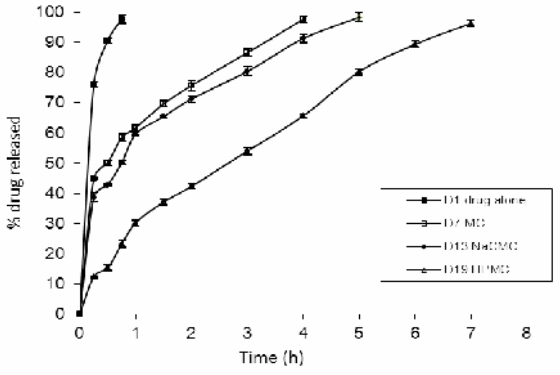

Fig. 4: Release profiles of isoxsuprine HCl from tablets containing 30% (w/w) of different hydrophilic polymers.

In order to highlight the differences found in the release profiles of the three different formulae (D7, D13 and D19) in addition to formula D1 containing drug alone, $t_{50\%}$ and $t_{90\%}$ have been calculated and their values are reported in table 5. $t_{50\%}$ and $t_{90\%}$ are the time needed for the release of 50% and 90% of the total amount of drug contained in the tablet. Formula (D19), containing 30% (w/w) HPMC 15000, showed the highest values of $t_{50\%}$ and $t_{90\%}$ and this confirmed that isoxsuprine HCl tablets prepared using 30% (w/w) HPMC 15000 gave the most sustaining effect of isoxsuprine HCl release among the studied hydrophilic polymers. Generally, it could be observed that the release of isoxsuprine HCl from all the prepared formulations in acidic medium was pronouncedly more rapid than in phosphate buffer (pH 6.8). This initial rapid release of isoxsuprine HCl from the sustained release tablets in pH 1.2 may be attributed to the presence of the drug in higher concentration in the ionized form (salt form), which has higher solubility than the base, hence the drug particles close to the tablet surface might be released first giving this initial higher release of the drug[14]. Moreover, the viscosity of the gel layer around the drug may decrease in acidic medium. By increasing the pH of the dissolution medium, more sustaining drug release was obtained and this may be due to the increase in the viscosity of the gel layer[14].

Table 5: $t_{50\%}$ and $t_{90\%}$ of isoxsuprine HCl tablets containing 30% (w/w) of different hydrophilic polymers.

Formula number	Polymer	$t_{50\%}$ (hour)*	$t_{90\%}$ (hour)**
D1	---	0.04	0.50
D7	MC	0.50	3.50
D13	Na CMC	0.75	3.75
D19	HPMC 15000	2.58	6.25

*$t_{50\%}$: Time for release 50% of the drug contained in the tablet.

**$t_{90\%}$: Time needed for release 90% of the drug contained in the tablet.

Figures 5-9 show the effect of different ratios of the investigated hydrophobic polymers on isoxsuprine HCl release from the prepared tablets using pH-shift method[8].

Figure 5 shows the release profiles of isoxsuprine HCl from the prepared tablets containing different ratios of EC. The drug release decreased upon the incorporation of EC. This decrease may be attributed to the nature of EC, which is a hydrophobic cellulose ether that forms a thick coat around the drug particles.

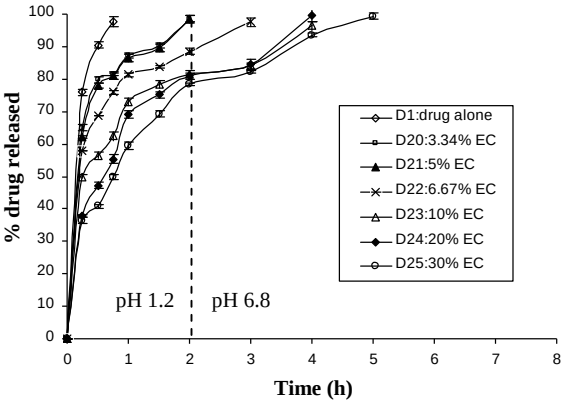

Fig. 5: Release profiles of isoxsuprine HCl from tablets containing different ratios of ethyl cellulose.

Upon contacting with the dissolution medium, diffusion and dissolution of the drug through water filled capillaries within the pore[15]. The release rate of isoxsuprine HCl decreased as the percent of EC increased from 3.34 to 30% (w/w). This increase in the sustaining of the drug release may be due to the increase in the thickness of the insoluble EC coat formed around the drug particles. The maximum sustaining, about 5 hrs, of the drug release was obtained from formula D25 containing 30% (w/w) EC.

Figure 6 illustrates the release profiles of isoxsuprine HCl from tablets prepared using Eudragit RL100. It is clear from this figure that the drug release decreased as the percent of Eudragit RL100 increased and the maximum release duration (5 hrs) was obtained in case of formula D31, containing the drug and 30% (w/w) Eudragit RL100. This decrease in the drug release may be attributed to the nature of Eudragit RL100, which is an acrylic copolymer that forms water-insoluble coat with defined permeability to water and to dissolved drugs.

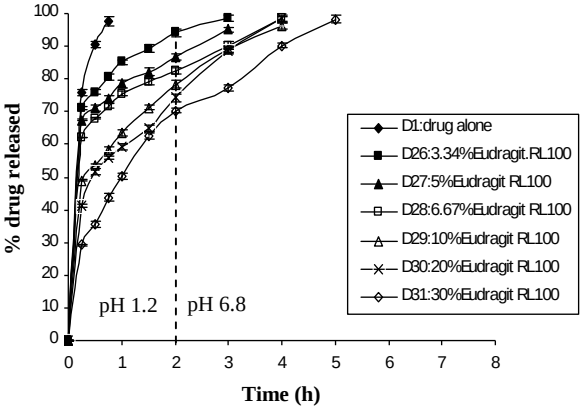

Fig. 6: Release profiles of isoxsuprine HCl from tablets containing different ratios of Eudragit RL100.

Figure 7 shows the release profiles of isoxsuprine HCl from tablets containing different ratios of Eudragit RS100. As shown in this figure, drug release is markedly decreased due to the presence of Eudragit RS100 that forms a low permeable coat around the drug particles. This coat has a relatively strong sustaining effect on drug release and the maximum retardation was obtained in case of formula D37 which contains 30% (w/w) Eudragit RS100.

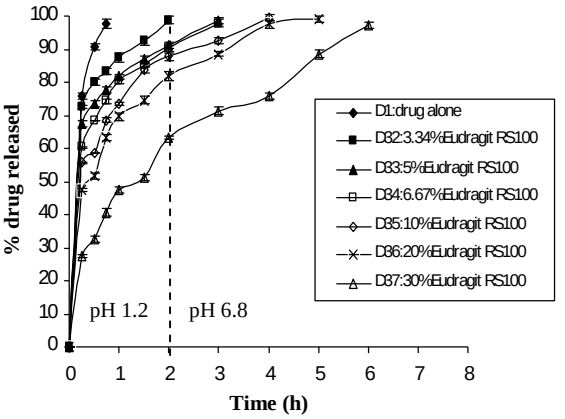

Fig. 7: Release profiles of isoxsuprine HCl from tablets containing different ratios of Eudragit RS100.

The effect of different percentages of Eudragit RSPM on the release of isoxsuprine HCl from the prepared tablets is shown in figure 8. It is clear that the drug release was markedly decreased when the percentage of Eudragit RSPM increased in the tablet formulation. The complete drug release was obtained after 8 hrs in case of formula D43 containing 30% (w/w) of this polymer.

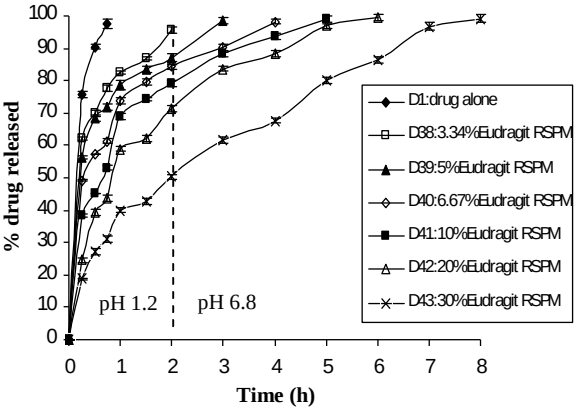

Fig. 8: Release profiles of isoxsuprine HCl from tablets containing different ratios of Eudragit RSPM.

Figure 9 shows the release profiles of isoxsuprine HCl from tablets prepared using different ratios of Eudragit RLPO. The release of isoxsuprine HCl from these tablets decreased by increasing the polymer content in the tablet.

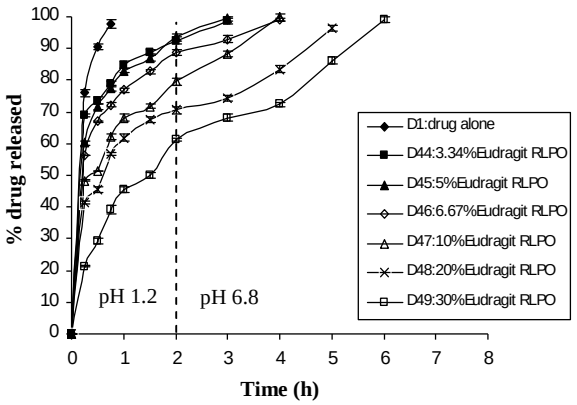

Fig. 9: Release profiles of isoxsuprine HCl from tablets containing different ratios of Eudragit RLPO.

Figure 10 shows the drug release profiles of isoxsuprine HCl from tablets containing 30% (w/w) of different hydrophobic polymers. It is clear that the sustaining effect of the investigated hydrophobic polymers on the drug release can be arranged in the following descending order: Eudragit RSPM > Eudragit RLPO > Eudragit RS100 > Eudragit RL100 > EC. The maximum retardation effect on the drug release was obtained in case of Eudragit RSPM and this may be attributed to its pH-independent solubility properties and the low permeability to water-soluble drugs[16].

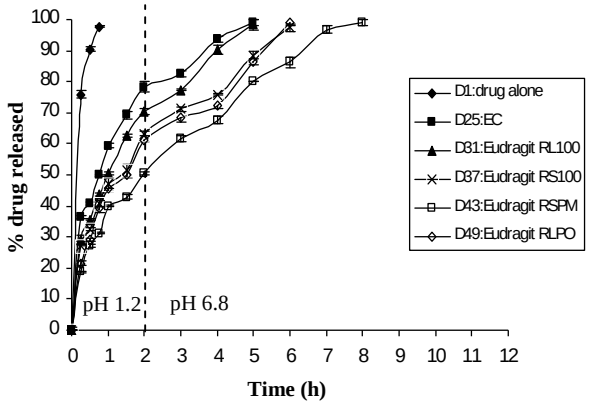

Fig. 10: Release profiles of isoxsuprine HCl from tablets containing 30% (w/w) of different hydrophobic polymers.

Table 6 shows $t_{50\%}$ and $t_{90\%}$ values of isoxsuprine HCl release from tablets containing 30% (w/w) of different hydrophobic polymers. It is clear that tablet formula (D25) containing EC has the least $t_{50\%}$ and $t_{90\%}$ values among the studied hydrophobic polymers. Tablet formula (D43) containing Eudragit RSPM shows the highest $t_{50\%}$ and $t_{90\%}$ values and this confirmed that isoxsuprine HCl tablets prepared using 30% (w/w) Eudragit RSPM gave the most sustaining effect on the drug release among the studied hydrophobic polymers. Isoxsuprine HCl tablets containing 30% (w/w) Eudragit RS100 (formula D37) show more sustaining of drug release than those containing 30% (w/w) Eudragit RL100 (formula D32) and this may be attributed to that Eudragit RS100 has lower permeability to the aqueous solution and the active ingredient than Eudragit RL100. Generally, RS type of Eudragits has low permeability to aqueous solutions due to its lower content in quaternary ammonium functional groups which give rise to the permeability of the coat and the ammonium/meth-acrylic acid ester values are 1/40 and 1/20 for Eudragit RS- type and Eudragit RL- type, respectively[16].

Table 6: $t_{50\%}$ and $t_{90\%}$ of isoxsuprine HCl tablets containing 30% (w/w) of different hydrophobic polymers.

Formula number	Polymer	$t_{50\%}$ (hour)*	$t_{90\%}$ (hour)**
D1	---	0.04	0.50
D25	EC	0.75	3.50
D31	Eudragit RL100	1.00	4.00
D37	Eudragit RS100	1.40	5.25
D43	Eudragit RSPM	2.00	6.58
D49	Eudragit RLPO	1.50	5.50

*$t_{50\%}$: Time for release 50% of the drug contained in the tablet.

**$t_{90\%}$: Time needed for release 90% of the drug contained in the tablet.

The release profiles of isoxsuprine HCl from the prepared tablets containing different polymer blends are shown in figures 11-15.

The effect of different ratios of NaCMC on isoxsuprine HCl release from tablets containing 10% (w/w) HPMC 15000 is illustrated in figure 11. It is clear that the isoxsuprine HCl matrix tablet prepared with a combination of Na CMC (ionic hydrophilic polymer) and HPMC 15000 (non ionic hydrophilic polymer) gave slower release of the drug than tablets prepared using 10% (w/w) HPMC 15000 alone, formula (D17). This may be due to the fact that, when the matrix tablet prepared using hydrophilic polymer comes into

contact with water, it swells and forms a porous gel barrier, the pores near the surface of matrix are filled with water. The drug release is initially controlled by the dissolution of the drug in the water filled pores and then by diffusion[17&18]. The presence of NaCMC in the polymer blend resulted in the formation of a highly viscous solution in the pores up on dissolution, which in turn slowed down the drug release by the formation of an additional gel-like barrier. As shown in figure 11, as the percentage of NaCMC increased in the polymer blend used for the preparation of isoxsuprine HCl matrix tablets, the synergistic retardation effect of the polymer blend increased and a valuable decrease of drug release rate can be achieved.

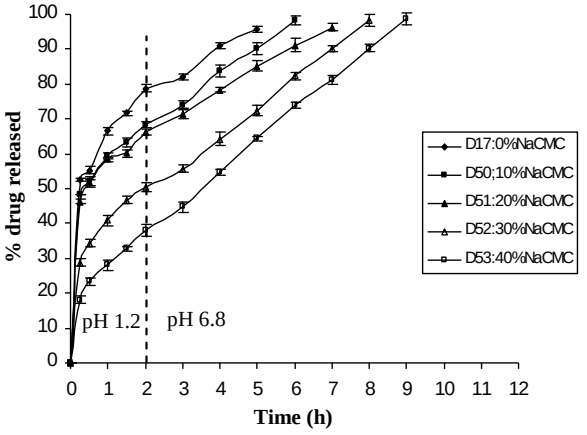

Fig. 11: Release profiles of isoxsuprine HCl from tablets containing 10% (w/w) HPMC 15000 and different ratios of sodium carboxymethyl cellulose.

Figure 12 shows the release profiles of isoxsuprine HCl from tablets containing 10% (w/w) HPMC 15000 and different ratios of EC. The drug release from tablets containing the polymer blend was less than that from tablets containing HPMC 15000 alone and this may be attributed to the presence of EC, which is a hydrophobic polymer, the admixture of HPMC with EC could change the permeability of the prepared matrix and consequently modify the release rate of the drug[19]. The maximum sustaining drug release was obtained from tablet formula: D57 that contains isoxsuprine HCl, 10% (w/w) HPMC 15000 and 40% (w/w) EC.

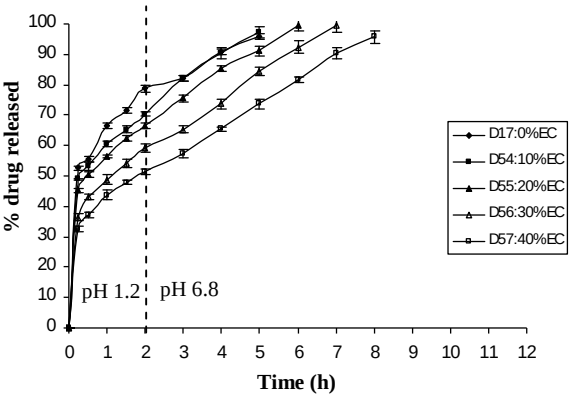

Fig. 12: Release profiles of isoxsuprine HCl from tablets containing 10% (w/w) HPMC 15000 and different ratios of ethyl cellulose.

Figure 13 illustrates the drug release profiles of isoxsuprine HCl from tablets containing 10% (w/w) HPMC 15000 and different percentages of Eudragit RSPM. It is clear from the figure that there was a marked decrease in the release of isoxsuprine HCl from the prepared sustained release tablets containing the blend of HPMC and Eudragit RSPM. Eudragit RSPM is a pH independent polymer with poor surface wettability and low swelling properties. Therefore, its combination with HPMC 15000 can result in a pronounced sustaining of drug release. As the percentage of Eudragit RSPM increased, the drug release decreased and the maximum drug release retardation was obtained when the blend of 10% (w/w) HPMC 15000 and 40% (w/w) Eudragit RSPM (formula D61) was used. The total drug release from this tablet formula was obtained after 12 hrs.

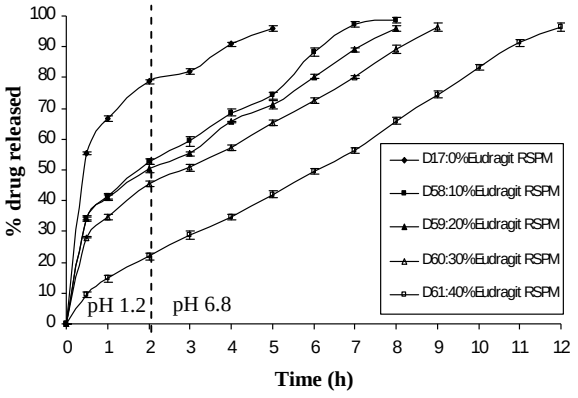

Fig. 13: Release profiles of isoxsuprine HCl from tablets containing 10% (w/w) HPMC 15000 and different ratios of Eudragit RSPM.

The effect of different weight ratios of EC on the drug release from tablets containing 10% (w/w) Eudragit RSPM is shown in figure 14. Results showed that the blend of EC and Eudragit RSPM at different percents reduced the drug release more than Eudragit RSPM alone (formula D41). It is clear from the figure that as the percentage of EC increased, the drug release from the prepared tablets decreased. The maximum time for total drug release (9 hrs) was obtained when 40% (w/w) EC was added to isoxsuprine HCl tablets containing 10% (w/w) Eudragit RSPM (formula D65).

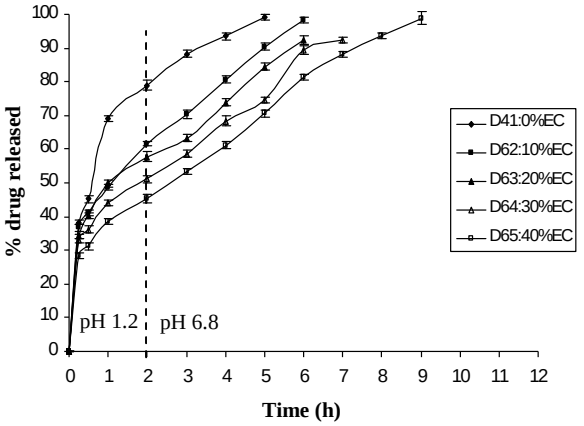

Fig. 14: Release profiles of isoxsuprine HCl from tablets containing 10% (w/w) Eudragit RSPM and different ratios of ethyl cellulose.

Figure 15 shows the drug release profiles of isoxsuprine HCl from tablets containing 10% (w/w) Eudragit RSPM and different ratios of Eudragit RLPO. It is clear that there was a marked decrease in the drug release from tablets containing different ratios of the polymer blend than the drug release from tablets containing 10% (w/w) Eudragit RSPM alone. This may be attributed to the synergistic retardation effect of the two hydrophobic polymers used.

As shown from figure 15, as the ratio of Eudragit RLPO increased from 10% (w/w) to 40% (w/w), the sustaining effect on the drug release increased. Tablets containing 10% (w/w) Eudragit RSPM and 40% (w/w) Eudragit RLPO (formula D69) gave the least drug release and the total drug release was achieved after 12 hrs.

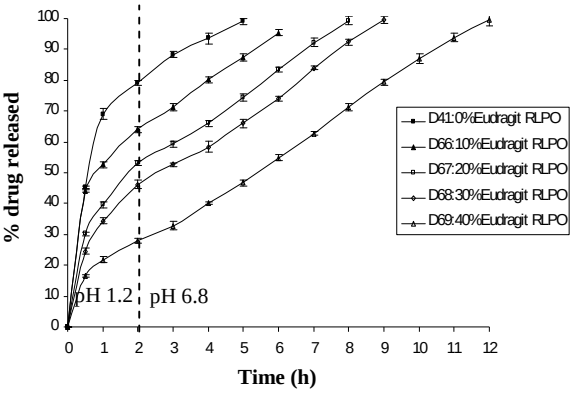

Fig. 15: Release profiles of isoxsuprine HCl from tablets containing 10% (w/w) Eudragit RSPM and different ratios of Eudragit RLPO.

Table 7 shows $t_{50\%}$ and $t_{90\%}$ values of isoxsuprine HCl release from tablets containing different polymer blends. It is clear that isoxsuprine HCl sustained release tablets containing single polymers (formulae D17 and D41) have the least values of $t_{50\%}$ and $t_{90\%}$. Isoxsuprine HCl sustained release tablets containing the blend of 10% (w/w) HPMC 15000 and 40% (w/w) Eudragit RSPM (formula D61) as well as those containing the polymer blend of 10% (w/w) Eudragit RSPM and 40% (w/w) Eudragit RLPO (formula D69) have the highest value of $t_{50\%}$ and $t_{90\%}$ among the studied formulae. From the results obtained it is clear that these two types of polymer blends are preferable for the design of the oral sustained release product of isoxsuprine HCl, where the rate of the drug release was remarkably prolonged.

Table 7: $t_{50\%}$ and $t_{90\%}$ of isoxsuprine HCl tablets containing different polymer blends.

Formula number	Polymer	$t_{50\%}$ (hour)*	$t_{90\%}$ (hour)**
D17	10% (w/w) HPMC 15000	0.20	4.00
D41	10% (w/w) Eudragit RSPM	0.70	3.75
D53	10% (w/w) HPMC + 40% (w/w) Na CMC	3.50	7.75
D57	10% (w/w/) HPMC + 40% (w/w) EC	2.75	7.00
D61	10% (w/w) HPMC + 40% (w/w) Eudragit RSPM	6.07	10.85
D65	10% (w/w) Eudragit RSPM + 40% (w/w) EC	2.50	7.75
D69	10% (w/w) Eudragit RSPM + 40% (w/w) Eudragit RLPO	5.42	10.54

*$t_{50\%}$: Time for release 50% of the drug contained in the tablet.
**$t_{90\%}$: Time needed for release 90% of the drug contained in the tablet.

The kinetic parameters for the *in-vitro* release of isoxsuprine HCl from the prepared sustained release tablets were determined and analyzed in order to explain the mechanism of the drug release It is clear that the release of isoxsuprine HCl from all the prepared sustained release tablets containing single polymers in the both dissolution media are best fitted to simplified Higuchi model as indicated from the highest regression coefficient (r^2). This means that the release rate of isoxsuprine HCl from the prepared sustained release tablets (formulae D2-D49) is dependent on the diffusion mechanism.

The release data of isoxsuprine HCl from tablets containing different polymer blends in dissolution medium of pH 1.2 were best fitted to simplified Higuchi model indicating that the release of the drug is dependent on the diffusion of the drug through the polymer gel layer. In dissolution medium of pH 6.8, the release of isoxsuprine HCl from sustained release tablets containing the blend of HPMC 15000 with either NaCMC or Eudragit RSPM, in addition to the blend of Eudragits RSPM and RLPO followed zero-order release mechanism. This may be attributed to the sufficient sustaining of the drug release due to the presence of polymer blends that leads to increase in the total polymer content resulted in highly viscous gel layer around the drug leading to zero-order drug release. As one of the major objectives in the development of sustained release drug delivery system is to prepare devices, which release drugs at a constant rate for extended period of time. In order to obtain a constant blood level for certain desired period. In this study, Tablet formulae D61 and D69 sustained isoxsuprine HCl release for 12 hrs and the mechanism of this drug release is zero-order release kinetics.

REFERENCES

1- P. Borgquist, A. Körner, L. Piculell, A. Larsson and A. Axelsson, "A model for the drug release from a polymer matrix tablet-effects of swelling and dissolution", J. Control. Release, 113 (3), 216-225 (2006).

2- N. K. Ebube and A.B Jones, "Sustained release of acetaminophen from a heterogenous mixture of two hydrophilic non-ionic cellulose ether polymers", Int. J. Pharm., 272, 19 (2004).

3- F. Siepmann, J. Siepmann, M. Walther, R.J., MacRae and R. Bodmeier, "Polymer blends for controlled release coatings", J. Control. Release, 125 (1), 1-15 (2008).

4- S. Strübing, H. Metz and K. Mäder, "Mechanistic analysis of drug release from tablets with membrane controlled drug delivery", Eur. J. Pharm. Biopharm., 66, 113-119 (2007).

5- F. Lecomte, J. Siepmann, M. Walther, R. J. MacRae and R. Bodmeier, "Blends of enteric and GIT-insoluble polymers used for film coating: physicochemical characterization and drug release patterns", J. Control Release, 89, 457-471 (2003).

6- A. Dashevsky, K. Kolter and R. Bodmeier, "pH-independent release of a basic drug from pellets coated with the extended release polymer dispersion kollicoat SR 30 D and the enteric polymer dispersion Kollicoat MAE 30 DP", Eur. J. Pharm. Biopharm., 58, 45-49 (2004).

7- USP XXV, 25th ed., Convention, INC., Rockville, M.D., 2002, p. 799.

8- S. Y. Lin and Y. H. Kao, "Effect of eudragit and dibasic calcium phosphate on the compaction and dissolution behaviour of directly compressible controlled-release theophylline tablet", Drug Dev. Ind. Pharm., 16 (5), 855-874 (1990).

9- A. Sh. Ali, A. M. Ali and F. A. Mohammed, "Formulation and evaluation of controlled release aminophylline matrix tablets", Bull. Pharm. Sci. Assiut University, 20 (2), 141-146 (1997).

10- I. El-Gibaly and E. M. Samy, "Development and evaluation of a prolonged-release matrix tablets of diclofenac sodium resinate", ibid., 21 (2), 184-202(1998).

11- S. Conti, L. Maggi, L. Segale, E. Ochoa Machiste, U. Conte, P. Grenier and G. Vergnault, "Matrices containing NaCMC and HPMC 1: Dissolution performance characterization", Int. J. Pharm., 333, 136-142 (2007).

12- A. Miranda, M. Milan and I. Caraballo, "Study of the critical points of HPMC hydrophilic matrices for controlled drug delivery", ibid., 311, 75-81 (2006).

13- A. Savaser, Y. Ozken and A. Isimer, "Preparation and *in-vitro* evaluation of sustained release tablet formulations of diclofenac sodium", Il Farmaco, 60, 171-177 (2005).
14- P. S. Hiremath and R. N. Soha, "Oral matrix tablet formulations for concomitant controlled release of anti-tubercular drugs: design and *in-vitro* evaluation", Int. J. Pharm., 362, 118-125 (2008).
15- A. K. Bajpai, S. Shukla, S. Bhanu and S. Kankane, "Responsive polymers in controlled drug delivery", Progress in Polymer Science, 33 (11), 1088-1118 (2008).
16- M. A. Khan and I. K. Reddy, "Controlled drug delivery development of solid oral dosage forms with acrylate polymers", S.T.P. Pharm. Sciences, 6, 483-489 (1997).
17- R. Gurny, E. Dolleker and N. A. Peppas, "Modeling of sustained release of water-soluble drugs from porous, hydrophobic polymers", Biomaterials, 3, 27-32 (1982).
18- R. Krosmeyer, R. Gurny, E. Dolleker, P. Buri and N. A Peppas, "Mechanisms of solute release from porous hydrophilic polymers", Int. J. Pharm., 15, 25 (1983).
19- M. A. Dabbagh, J. L. Ford, M. H. Rubinstein and J. E. Hogan, "Effects of polymer particles size, compaction pressure and hydrophilic polymers on drug release from matrices contain ethyl cellulose", ibid., 140, 85-95(1996).