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INFLUENCE OF CERTAIN ADSORBENTS ON THE *IN VITRO* AVAILABILITY OF LIDOCAINE FROM SOME SUPPOSITORY BASES

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يعتبر الليدوكايين من العقاقير المفضلة فى علاج اختلال ضربات القلب وفى الوقاية من بوار عضلة القلب بالإضافة إلى أنه يعد من أكثر مواد التخدير الموضعية استعمالا ولكن تحول بعض المشاكل صياغة العقار فى بعض الأشكال الصيدلية المختلفة لعدم إمكانية تناول العقار عن طريق الفم لتعرضه للأيض الكبدى الأولى وقصر العمر النصفى للعقار ووجوده فى صورة متأينة (هيدروكلوريد الليدوكايين) فى المستحضرات الصيدلية والتى تقلل من الإتاحة الحيوية للعقار. وللتغلب على ذلك فقد أجريت عدة محاولات بحثية لصياغة الليدوكايين فى أقماع شرجية لتفادى الأيض الكبدى الأولى وتحسين معدل الانطلاق المعملى لتحقيق أكبر معدل اتاحة للدواء.

تتناول الدراسة تحضير مشتتات صلبة مع بعض المواد المازة (فلوريت آر - أفيسيل PH 102) بنسب وزنية مختلفة وتم دراسة الامتزاز السطحى بين العقار والمواد المازة بواسطة طرق التحليل الفيزوكيميائية المختلفة: الأشعة السينية والأشعة تحت الحمراء والمسح الحرارى التفاضلى وقد أوضحت النتائج أن المواد المازة المستخدمة تؤثر بدرجة كبيرة على الترابط أو التداخل بين جزئيات العقار وجزئيات المادة المازة وزيادة معدل إذابة العقار من المشتتات الصلبة.

وأشتملت الدراسة تحضير أقماع شرجية حاملة للعقار والمشتتات الصلبة وتم دراسة الخواص الفيزيائية ومعدل الانطلاق المعملى للأقماع المحضرة سابقا. أثبتت الدراسة أن معدل الانطلاق المعملى للعقار المتواجد فى صورة مشتت صلب أعلى من العقار منفردا. كما أوضحت الدراسة أن معدل الانطلاق المعملى من قواعد الأقماع الشرجية التى تذوب فى الماء أعلى من الانطلاق المعملى من قواعد الأقماع المحضرة من مواد شبه مخلقة. وعلى ضوء هذه الدراسة تبرز أهمية استخدام المشتتات الصلبة كواحدة من الطرق الفاعلة لتحسين إذابة الأدوية وزيادة معدل الانطلاق المعملى.

The effect of porous calcium silicate (Florite R) and microcrystalline cellulose (Avicel PH 102) on the physicochemical characterizations and dissolution rate of lidocaine (LD) and consequently the effect on the in vitro availability of LD from some suppository bases has been studied. The solid dispersions (sorbates) of LD with the previous adsorbents were prepared by the solvent deposition method. The characterizations of sorbates were established by X-ray, differential thermal analysis (DTA) and IR-spectroscopy. The X-ray diffraction results indicate reducing the crystallinity of LD. The thermograms of DTA indicate a weak and reversible endothermic interaction between LD and the previous adsorbents. The dissolution rate of LD from its physical mixtures and sorbates, in various ratios (1:1, 3:2, 4:1 and 9:1 w/w) were studied. The results showed that LD/Florite R sorbate in 3:2 w/w ratio achieved the best dissolution rate.

In vitro availability of LD from some water-soluble bases (polyethylene glycols) and fatty bases (Witepsol H 15 and Suppocires AM and CM) has been studied by using a diffusion cell with artificial membrane at 37°C. The release of LD was significantly faster from water-soluble bases containing LD/Avicel PH 102 sorbate. Also, it appeared that increasing the proportion of low molecular weight polyethylene glycols in the suppository formulation had greater effect on the rate and extent of release and diffusion of the drug through the membrane.

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INTRODUCTION

Lidocaine (LD), originally developed as a local anesthetic, was introduced as an antiarrhythmic agent in 1962 for the emergency treatment of ventricular arrhythmia. Lidocaine undergoes extensive first pass metablism.[1] This property makes it unsuitable for oral administration. At the same time, its use intravenously is restricted because of the short elimination half-life. This necessitates the parenteral route to be carried out only in the medical centers under certain precautions to overcome the overlap between the plasma therapeutic levels (1.5-5.5 μg/ml) and the range of the objective adverse manifestation levels (6-10 μg/ml).[2-6]

To overcome the previous problems some investigators have designed rectal formulations and reported that the bioavailability of LD after rectal administration is substantially higher than after oral administration.[7-10] The efforts, in any way, must be continued for preparing rectal suppositories of LD to avoid the toxicity of too prolonged intravenous infusion time and the ineffectiveness of the oral administration.

In this work, LD base (unionized form) was selected instead of the salt form (ionized form), in spite of the free solubility of the salt form, because of the poor bioavailability of the salt.[11] Solid dispersion technique was used to enhance dissolution rate, which consequently improve the rate and extent of drug availability.

EXPERIMENTAL

Materials

Lidocaine base was obtained as gift from Astra scientific office in Egypt (Astra Co., Sweden). The following chemicals were obtained from commercial suppliers and used as received: Florite R (Tokuyama Soda, Japan), Avicel PH 102 (FMC Co., Ireland), Witepsol H15 (Dynamit Nobl Co., Germany) and Suppocires AM and CM (EMB Co., France). Standard cellophane membrane; 30/32 was obtained from Sigma Chemical Co. (USA). All other chemicals were commercially available products of reagent grade.

Methods

Preparation of LD sorbates

Initially, the different adsorbents were sieved, using set sieve shaker, RX-86-1 (Cole-Parmer Instrument Co., USA). Florite R of average particle size passed through 230 μm sieve, was dried in vacuum at 0.1 mmHg and 120°C for 3 hours. Avicel PH 102 of average particle size passed through 80 μm sieve, was dried in vacuum at 0.1 mmHg and 70°C for 24 hours.

Solid dispersions of LD, which has high thermal stability and Florite R or Avicel PH 102 in ratio 1:1, 3:2, 4:1 and 9:1 w/w were prepared, using solvent-evaporation technique, in chloroform to give the required ratios. The mixtures were dried under reduced pressure at 45°C using rotary evaporator, type vv 2000 (Heidolph, Germany). The solid dispersions were further dried under vacuum at 30°C for 3 days and were grounded and sieved through 45 μm sieve. A specified sample of each prepared dispersion was assayed for its drug content. Only those samples containing 100±5% of the claimed amount of LD were used for further investigations.

Preparation of LD/adsorbents physical mixtures

Initially LD, Florite R and Avicel PH 102 were sieved to give average particle size passed through 45 μm sieve. Physical mixture in the previous ratios were prepared by simple mixing.

X-ray diffractometry

Powder X-ray diffraction patterns were obtained using a computer controlled Philips diffractometer mode 1710 (Philips Co., Netherland), operating in the 2θ mode to determine the physical nature of LD in the solid dispersins and physical mixtures. A Cu target tube operated at 40 Kv and 30 mA and a single crystal graphite monochromator were employed. The wave length of the Cu-Kα radiation, λ= 1.5418 A°, was used. Standard polycrystalline silicon powder was used to calibrate the equipment.

IR studies

IR spectra of the dried samples were obtained with an infra-red spectrophotometer, model IR-476 (Shimadzu Co., Japan) using KBr pellets prepared at a pressure of 6 ton/cm^2.

Differential thermal analysis (DTA)

Thermograms were recorded on a differential thermal analyzer, model DTA-50 (Shimadzu Co., Japan). All samples (6-8 mg) were heated in the aluminium DTA pans at a rate of 20°C/min from 30 to 200°C under atmosphere of dry nitrogen. The flow rate of the purging gas was 40 ml/min.

Dissolution rate studies

Dissolution tests were carried out with samples (solid dispersion and physical mixture) equivalent to 500 mg of LD in 250 ml distilled water using USP paddle dissolution-test apparatus, model SR11 6-flask (Hanson Co., USA) at 50 rpm and 37±0.5°C. The drug content in the withdrawn aliquots was analyzed by using spectrophotometer, model UV-1601 (Shimadzu Co., Japan) at 263 nm. Aliquots of drug-free solution were used as blank to avoid UV-absorption inteference of adsorbents.

Preparation of suppositories

Suppository formulations were prepared from semisynthetic fatty bases (Witepsol H15, and Suppocires AM and CM) and water-soluble bases by fusion method. Each suppository (2 g) contains 50 mg of LD in the form of plain drug or as 3:2 w/w LD/Adsorbent solid dispersion. The suppository formulations are displayed in Table 1.

Evaluation of the prepared suppositories

Weight variation

The weight variation was determined according to the B.P. 1993. The average weight was calculated by weighing 20 suppositories individually. The percent of deviation from the mean was subsequently determined.

Drug content

For each formula, eight medicated suppositories were individually placed in 250 ml conical flasks containing 25 ml of 0.1 N HCl and maintained at 37±0.5°C. After complete melting or dissolving of the suppositories, the volume was completed with the same medium to 100 ml and the containers were allowed to rotate in water-bath shaker at 37±0.5°C and 120 rpm for 15 minutes. Aliquots were withdrawn from the aqueous phase and appropriately diluted with 0.1 N HCl and assayed. Non-medicated suppositories were subjected to the same previous procedure to serve as a blank for spectrophotometric determinations.

Disintegration time

The disintegration or dissolution times of fatty or water-soluble suppositories consequently, were determined using melting-time tester, Type SSP (Erweka Co., Germany). The tester was connected with a thermostatically controlled water bath at 37°C. The time in minutes required for complete melting or dissolving of the suppository was recorded as the disintegration time.

Mechanical strength

After the storage of the tested suppositories in a refrigerator (3-5°C) overnight, the resistance to break was evaluated both immediately, and 2 hours after leaving the refrigerator using suppository hardness tester, Type SBT (Erweka Co., Germany).

***In-vitro* release of LD from suppositories**

The method adopted by Kassem *et al.*[12] was used. A cellophane membrane (4x3 cm), soaked in distilled water overnight, was streched firmly over the end of glass tube (28 mm internal diameter). A volume of 10 ml phosphate buffer (pH 7.6) was poured into the tube. The tube was suspended in 250 ml beaker containing 100 ml of the phosphate buffer (pH 7.6). The whole dialysis system was placed into water-bath shaker maintained at 50 strokes/min. and 37±0.5°C and one suppository was introduced into the tube. At time intervals, a volume of 5 ml was withdrawn from the beaker and replaced by an equal volume of the buffer warmed at 37±0.5°C. The drug concentration was determined spectrophotometrically at 263 nm.[13]

RESULTS AND DISCUSSION

X-ray diffraction patterns of untreated LD, Florite R, the physical and sorbate mixtures are shown in Figure 1. The diffraction patterns of LD showed numerous strong peaks indicating the higher degree of crystallinity. X-ray diffraction patterns of Florite R displays weak and diffuse peaks which indicate the lower degree of crystallinity of Florite R. For the sorbate, the relative intensities (I/I_0) of some peaks to LD give values 3-10 times as high as those for drug alone as shown in Table 2. The results indicate the possibility of a complex formation between the drug and Florite R. At the same time, the results indicate that, there is no clear interaction between LD and Florite R in their physical mixture. Figure 2 shows that Avicel has diffraction peaks indicating very low crystallinity of this carrier. For both physical and sorbate mixture new peaks were found as shown in Table 3. This may indicate a drug-carrier interaction, which was slight in the physical mixture and increased considerably in sorbate mixture.

IR spectra of some characteristic bands for LD, LD/Florite R and LD/Avicel PH 102 systems listed in Table 4. The characteristic bands are N-H, C=O and N-N. These bands observed in the spectrum of LD at 3245, 1662 and 1494 cm^{-1} respectively, still appear at the same positions, but show slight broadening and decrease in intensities in the physical and sorbate mixtures as shown in Figures 3 and 4. The results indicate no chemical interactions between LD and the adsorbents.

DTA thermogram of untreated LD (Figs. 5,6) showed a sharp endothermic peak with a transition beginning at 67.07°C and maximum melting point at 72.03°C. Avicel PH 102 exhibited shallow broad endothermic peak at approximately 100°C, which corresponds to the temperature of water evaporation. A second endothermic peak for Avicel occurs only above 280°C.[14] DTA thermogram of Florite R did not show any initial endothermic reaction. Thermograms of LD/Florite R systems (Fig. 5) showed endothermic transitions beginning at 55 and 64.5°C and maximum melting points of 68.88 and 66.16°C for hte physical and solid dispersed mixtures respectively. The shift in the temperatures of the transitions and melting points of the previous mixtures, in comparison with the untreated drug, indicates that, a reversible interaction occurred between LD and Florite R. Figure 6 showed similar shifting with LD/Avicel PH 102 systems, but at less extent. None of all previous samples showed any major additional or new peaks. Hence, these excipients can be considered compatible with LD. The changes in peaks of LD, in all the previous physical and solid dispersion mixtures indicate reversible and weak endothermic interactions expected between the hydroxyl and ether groups on the surface of the adsorbents, and the cloud of electrons around oxygen and nitrogen atoms of the carbonyl (C=O) and amide (-NH) groups of the drug.

Dissolution data of LD from its physical and sorbate mixtures with Florite R or Avicel PH 102 (9:1, 4:1, 3:2 and 1:1 w/w ratios) are illustrated in Tables 5 and 6. The dissolution data of LD from its physical and sorbate mixtures with Florite R at different ratios exhibited a great enhancement in the dissolution rate at 3:2 w/w ratio as shown in Figure 7. Also, it was noticed a greater dissolution rate of LD from the sorbate than the corresponding physical mixture. Similar results, but at less extent, were observed with Avicel PH 102 (Fig. 8). The enhancements of dissolution rate of LD may be due to the partial molecualr adsorption of LD onto the large surface area of the adsorbents. Also, the micronization of LD is suggested to decrease the particle size of the drug and consequently enhances the dissolution rate from the sorbates.

Release profiles of LD from fatty suppository bases, B1, B2 and B3 (Table 1) in phosphate buffer at pH 7.6 showed that the maximum percentage released of LD (24.66%) was observed with witepsol-based suppository (formula B1) containing LD/Florite R (Fig. 9). Release profile of the drug from water-soluble suppository bases, B4, B5 and B6, showed that formula B4 containing LD/Avicel PH 102

Table 1: Composition of suppository bases used (weight percent).

Suppository base	Number of formula					
	B1	B2	B3	B4	B5	B6
Semisynthetic:						
Witepsol H15	100	--	--	--	--	--
Suppocire AM	--	100	--	--	--	--
Suppocire CM	--	--	100	--	--	--
Water-soluble:						
PEG 400	--	--	--	--	--	60
PEG 1000	--	--	--	97	75	--
PEG 4000	--	--	--	3	25	40

Table 2: Comparison of (I/I_o) of some peaks for LD and its sorbate mixture with Florite R.

Peak	2θ	d (A°)	hkl	LD	Sorbate
				$(I/I_o)\%$	(I/I_o)
1	27.348	3.2611	421	12	35.7
2	28.758	3.1042	303	10	46.5
3	29.683	3.009	-124	5	56

Table 3: X-ray diffraction parameters of new peaks found in physical and sorbate mixtures of LD and Avicel PH 102.

Peak	Physical mixture			Sorbate mixture	
	2θ	d (A°)	$(I/I_o)\%$	d (A°)	$(I/I_o)\%$
1	9.173	9.565	4	9.4609	26
2	11.043	8.059	2	8.0118	8
3	25.356	3.497	15	3.5120	46

Table 4: IR spectra (cm^{-1}) for lidocaine, physical mixture and sorbate mixture with Florite R and Avicel PH 102.

Tested sample		Assigment		
		N-H	C=O	C-N
LD	Reported	3240	1660	1490
	Recorded	3245	1662	1494
LD/Florite R	Phys. mix.	3250	1661	1492
	Sorbate	3260	1661	1493
LD/Avicel PH 102	Phys. mix.	3250	1661	1492
	Sorbate	3250	1662	1493

Table 5: Dissolution data of lidocaine from its physical and sorbate mixtures at different percentages of Florite R.

Time/ min.	Percentage dissolved of LD from								
	LD	Physical mixtures with LD/Florite ratio of				Sorbate mixtures with LD/Florite ratio of			
	1:0	9:1	4:1	3:2	1:1	9:1	4:1	3:2	1:1
5	25.4	65.2	60.4	61.2	61.1	50.2	68.5	67.4	68.4
10	35.6	70.2	72.7	74.7	67.5	67.2	78.9	82.0	71.2
15	44.0	71.2	76.1	74.8	70.0	74.4	75.1	81.0	82.4
30	54.0	76.2	78.1	75.0	71.0	79.2	75.2	82.5	73.8
45	61.1	76.2	74.4	77.6	78.5	80.2	81.6	91.4	78.5
60	67.8	77.2	78.0	84.3	82.2	81.4	80.8	92.0	90.8

Table 6: Dissolution data of lidocaine from its physical and sorbate mixtures at different percentages of Avicel PH 102.

Time/ min.	Percentage dissolved of LD from								
	LD	Physical mixtures with LD/Avicel PH 102 ratio of				Sorbate mixtures with LD/Avicel PH 102 ratio of			
	1:0	9:1	4:1	3:2	1:1	9:1	4:1	3:2	1:1
5	25.4	34.8	35.7	36.2	35.8	50.6	55.8	64.3	65.3
10	35.6	50.3	50.0	49.8	47.0	63.3	65.9	74.1	71.5
15	44.0	58.7	57.5	59.6	57.3	68.2	71.0	76.8	73.1
30	54.0	65.9	68.4	68.7	65.7	74.7	76.8	79.6	79.7
45	61.1	73.6	73.4	72.6	70.1	77.3	80.2	82.4	82.5
60	67.8	77.4	75.0	77.5	72.5	79.5	81.5	84.9	83.1

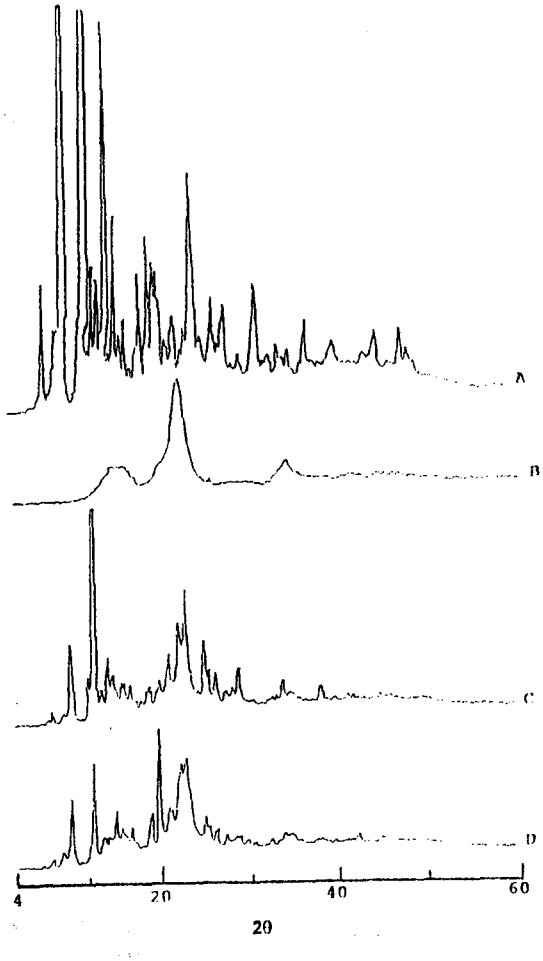

Fig. 1: X-ray diffraction patterns of LD/Florite R systems: (A) LD; (B) Florite R; (C) Physical mixture; (D) Sorbate mixture.

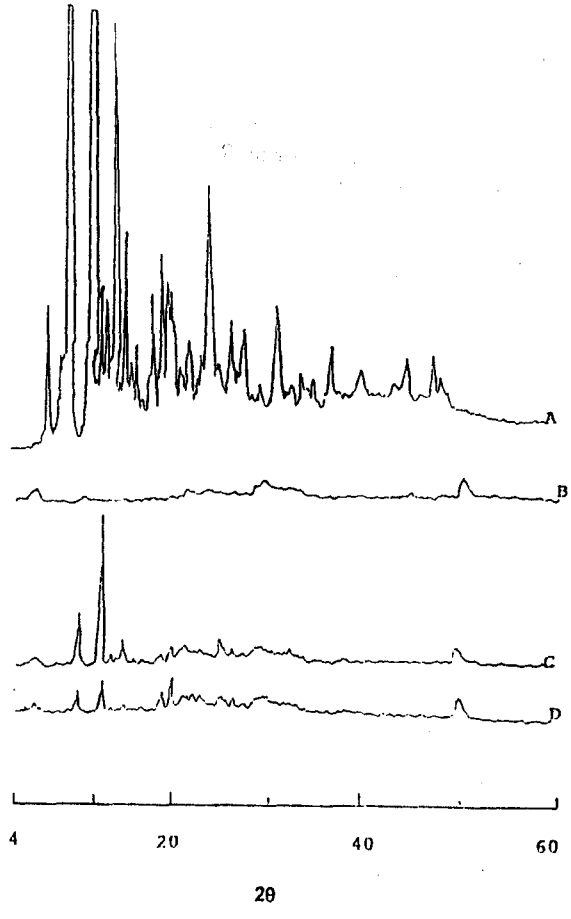

Fig. 2: X-ray diffraction patterns of LD/Avicel PH-102 systems: (A) LD; (B) Avicel PH-102; (C) Physical mixtures; (D) Sorbate mixture.

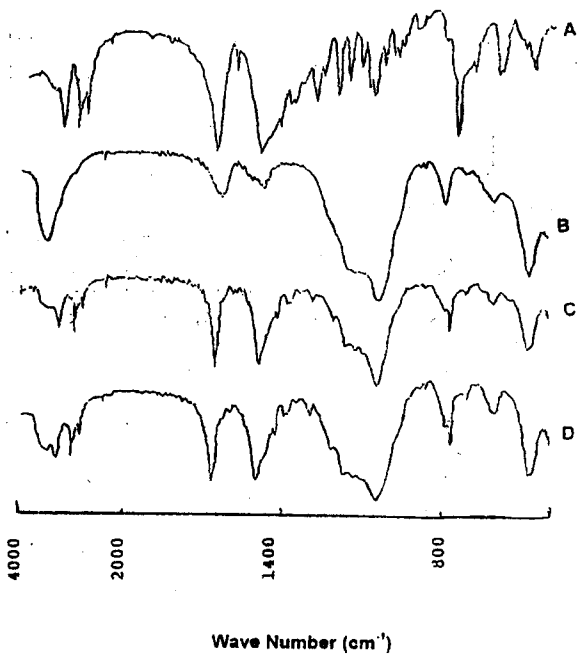

Fig. 3: IR spectra of LD/Florite R systems: (A) LD; (B) Florite R; (C) Physical mixture; (D) Sorbate mixture.

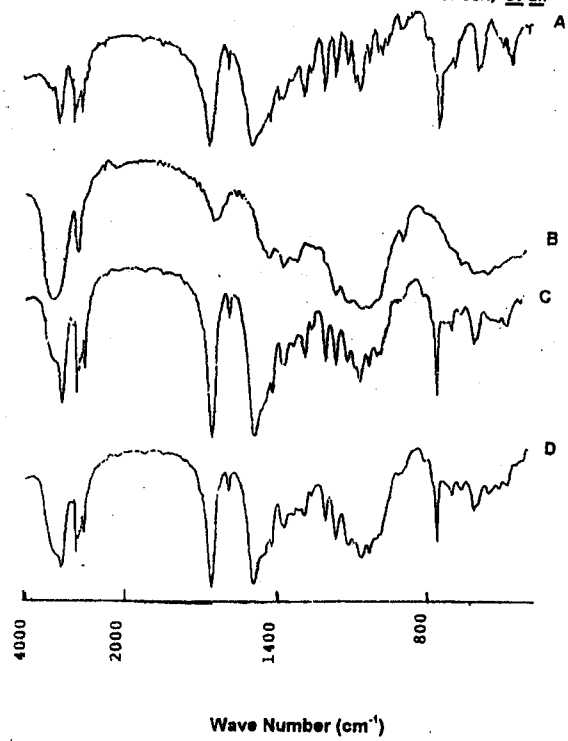

Fig. 4: IR spectra of LD/Avicel PH-102 systems: (A) LD; (B) Avicel PH-102; (C) Physical mixture; (D) Sorbate mixture.

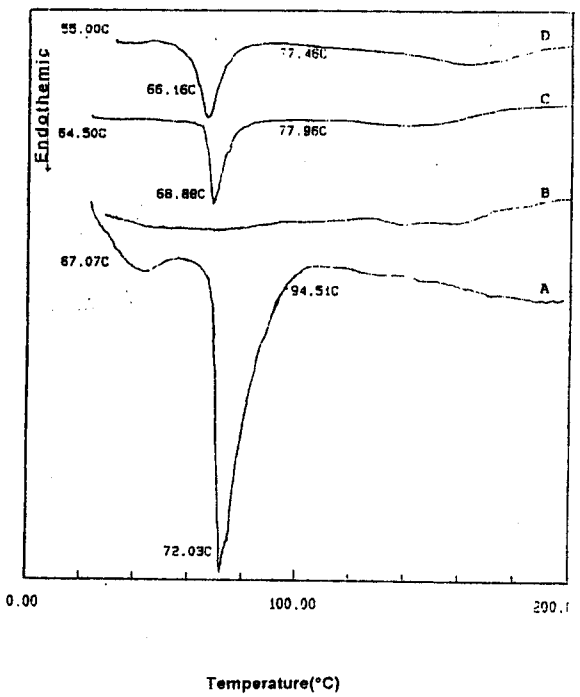

Fig. 5: DTA curves of LD/Florite R systems: (A) LD; (B) Florite R; (C) Physical mixture; (D) Sorbate mixture.

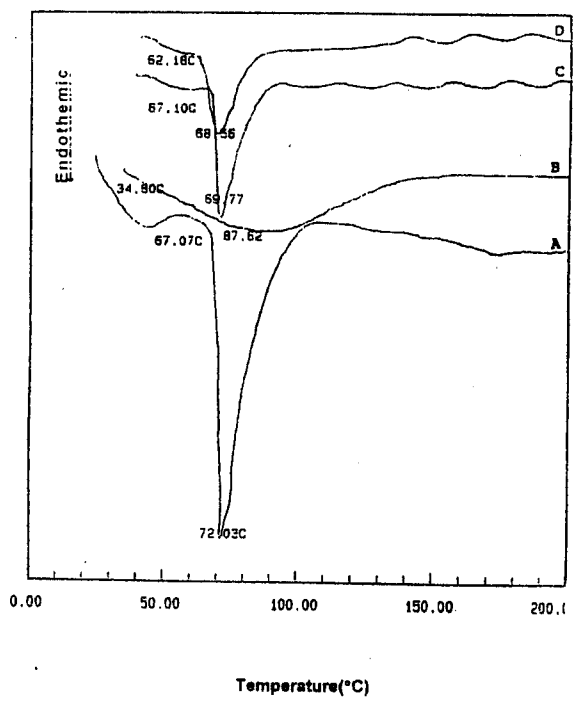

Fig. 6: DTA curves of LD/Avicel PH-102 systems; (A) LD; (B) Avicel PH-102; (C) Physical mixture; (D) Sorbate mixture.

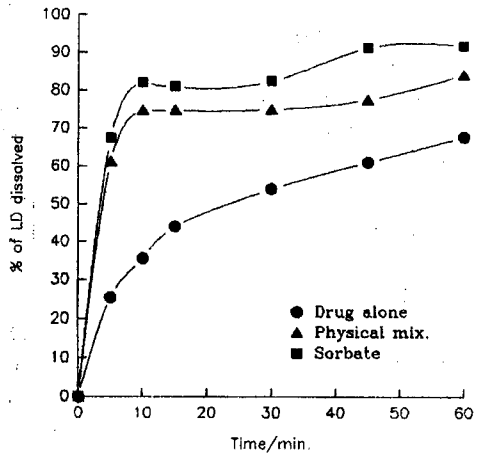

Fig. 7: Dissolution profiles of LD from the physical and the sorbate mixtures of 60% LD and 40% Florite R.

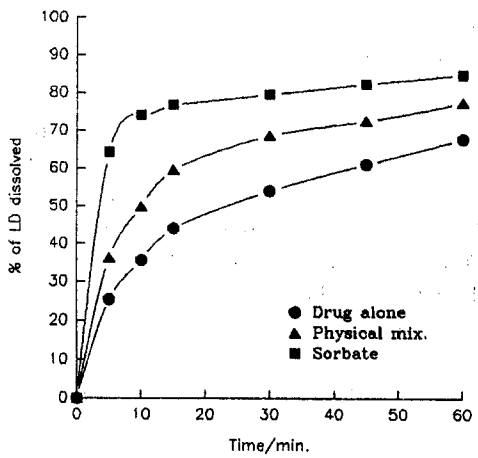

Fig. 8: Dissolution profiles of LD from the physical and the sorbate mixtures of 60% LD and 40% Avicel PH 102.

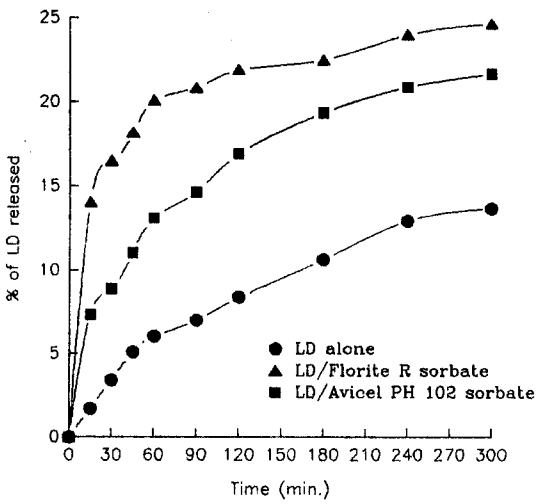

Fig. 9: Release profile of LD from formula B1.

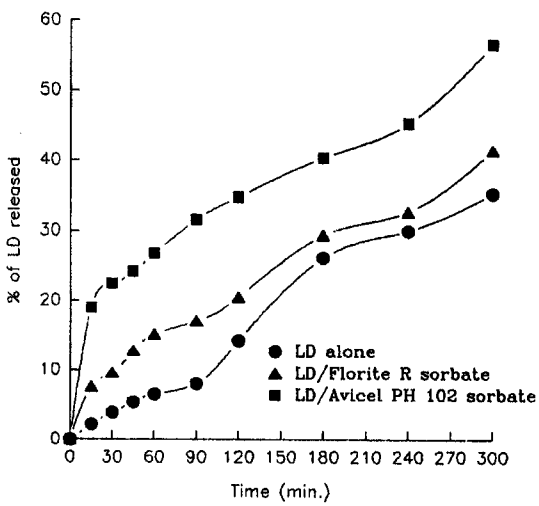

Fig. 10: Release profile of LD from formula B4.

sorbate (Fig. 10) achieved the maximum percentage released of LD (56.53%). The *in-vitro* release study revealed that the release rates of LD from suppositories containing LD sorbates were greater than from suppositories containing the drug alone. The enhanced release from water-soluble suppository bases containing LD/Avicel PH 102 sorbate may be attributed to enhanced dispersion and/or miscibility, and consequently the higher dissolution rate of the drug from its sorbate. In case of fatty bases, LD has high affinity to these bases and consequently low release rate.

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