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PREPARATION AND EVALUATION OF SUSTAINED RELEASE CARBAMAZEPINE MATRIX TABLETS USING EUDRAGIT RS 100 AND TRAGACANTH

M. O. Ahmed* and A. M. Aly

*Department of Industrial Pharmacy, Faculty of Pharmacy, Assiut University, Assiut, Egypt
Department of Industrial Pharmacy, Faculty of Pharmacy, Alisra University, Amman, Jordan

من المعروف أن دواء الكاربامزبين يستخدم فى علاج التشنج العصبى والصرع ، وقد وجد أنه يعطى اختلاف فى الامتصاص والكفاءة الحيوية. لهذا ينصح بتحضيره فى شكل دوائى ممتد الانطلاق لتحسين معاناة المريض والحصول على مستوى دم ثابت من العقار بأقل الأعراض الجانبية. قد تنشأ مشاكل مع تحضير أقراص الكاربامزبين بطريقة التحبب المبلل لو لم تكن الحبوب قد جففت تماما قبل الكبس. لذلك تختص هذه الدراسة بتطبيق طريقة الكبس المباشر فى تحضير أقراص مصفوفة للكاربامزبين ممتدة الانطلاق. ولقد اختبرت نسب مختلفة تتروح من صفر الى ٢٥٪ نسبة وزن من الايدراجت آر اس ١٠٠ والتراجاكنز لاختيار أحسن مستوى من هذه المواد التى تعطى أطول تأثير ممتد الانطلاق بعد تحضيرها بطريقة الكبس المباشر مستخدمين الافيسيل بى أتش ١٠٢ واللاكتوز كصواغات كبس مباشر. وقد وجد أن الأقراص المصفوفة بالكبس المباشر للكاربامزبين تطابقت مع مواصفات دستور الأدوية الامريكى رقم ٢٣ لسنة ١٩٩٥ من حيث تجانس الوزن والقطر والمحتوى الدوائى وكذلك الصفات الميكانيكية مثل قوة الشد والهشوشة. وقد تم فحص خصائص الانطلاق للكاربامزبين من تلك الأقراص ونوع حركية الانطلاق. ووجد أنه بزيادة نسبة البوليمر سواء ايدراجت أو تراجاكنز فى كل الصيغ من ٣,١٢٥ الى ٢٥٪ أدى الى نقص فى معدل انطلاق الدواء. وقد أعطى اندماج الايدراجت آر اس ١٠٠ فى الأقراص المصفوفة بالكبس المباشر تأخير انطلاق الكاربامزبين أكثر من اندماج التراجاكنز فى الوسط الحمضى ذو الرقم الايدروجينى ١,٢ والوسط المنظم للفوسفات ذو الرقم الايدروجينى ٦,٨ ، وهذا يعزى الى اختلاف الصفات الفيزيوكيميائية للبوليمر الطبيعى (التراجاكنز) عن البوليمر الصناعى (الايدراجت). وقد وجد بالمقارنة أن صيغة أقراص الكاربامزبين التى تحتوى على نسبة ٢٥٪ من التراجاكنز قد أعطت نفس سلوك الانطلاق لأقراص التجريتول. وقد أشارت قيم (إن) لمعادلة الانطلاق بأن حركية انطلاق الكاربامزبين من الأقراص المصفوفة تتبع الانتشار الغير عادى.

Carbamazepine is a widely prescribed anticonvulsant antiepileptic drug which shows variable absorption and variable bioavailability. It is advisable to prepare it in sustained release dosage form to improve patient compliance and to perform constant blood level with minimum side effects. Problems may be encountered with carbamazepine tablets prepared by wet granulation if the granules are not thoroughly dried before processing. Therefore, the present study deals with the application of direct compression technique to prepare sustained release carbamazepine matrix tablets. Different levels (0 to 25 %w/w) of Eudragit RS 100 and Tragacanth were tested to select the best level of matrix forming material that provides the most release prolonging effect, by direct compression technique using Avicel PH 102 and anhydrous lactose as directly compressible vehicles. Directly compressed matrix tablets of carbamazepine were found to be complied with the USP/ NF 23 requirements for the uniformity of weight, diameter, and acceptable mechanical properties with respect to tensile strength and friability. Examination of the release characteristics of the drug from the directly compressed tablets as well as the determination of the release mechanism were carried out. It was found that, as the percentage of the polymer (either Eudragit or Tragacanth) in all formulations increased from 3.125% to 18.75% or 25 %w/w, the drug release decreased significantly.

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Involvement of Eudragit RS 100 in the directly compressed matrix tablets gave more sustaining release of carbamazepine than inclusion of Tragacanth in both acidic medium (pH 1.2) and phosphate buffer medium (pH 6.8). This was due to the difference between the physicochemical properties of natural polymer Tragacanth and synthetic polymer Eudragit. Comparatively, the formula of carbamazepine tablet containing 25 %w/w Tragacanth showed similar release behaviour to that of the commercial Tegretol® tablets. The calculated exponential release exponents (n values) indicated that release behaviour of carbamazepine matrix tablets was anomalous (non-Fickian) diffusion kinetics.

INTRODUCTION

Hydrophilic matrices and swellable controlled release systems have become now popular in the formulation of controlled release solid dosage forms, mainly due to their optimal performance and ease of manufacturing. Several hydrophilic polymers have been investigated for this purpose, such as hydroxypropylmethyl cellulose (HPMC) and sodium carboxymethyl cellulose (NaCMC).[1-8] Egg albumin (EA) has been evaluated as a swellable material for the production of controlled release tablets for aminophylline,[9] Ketorolac tromethamine,[10] and carbamazepine.[11] In general, the advantages of these swellable polymers are that they can accommodate a high percentage of the drug and the drug release rate is generally independent of process variable.[12] The mechanism of drug release from these hydrophilic systems have been studied.[8-14] Hydrophilic matrix tablets have been used extensively to produce sustained drug delivery by the gastro-intestinal route. The desirable characteristics of polymer systems used for drug delivery, whether natural or synthetic, are minimal effect on biological systems after introduction into the body.

Polyacrylate-polymethacrylate copolymers (Eudragits) are widely used as tablet adjuvant and coating polymers,[15] and were also used for the microencapsulation of paracetamol, indomethacin and theophylline.[16,17] Eudragit polymers have also recently received increased attention as microsphere wall materials.[15,18] Sustained release solid dispersions have been investigated using Eudragit RS and Eudragit RL as carriers and indomethacin as a model drug.[19] These polymers are inert to the digestive tract content, pH independent, and capable of swelling. Coevaporates of various compounds (nifedipine, digoxin, dipyridamole, griseofulvin) were prepared using enteric coating agents (CAP, CMEC, Eudragits) as inert carriers.[20,21] Carbopol (CP) is a polymer of acrylic acid and forms hydrogel in water or alkaline solution due to hydration of the carboxyl groups in its structure. For the controlled release of drugs, CP has been studied as a matrix material directly compressed together with hydroxypropyl-cellulose (HPC) or HPMC in tablets and for a solid dispersion.[22,23] Poly(ethylene oxide) (PEO) is a class of water soluble linear resin, and has recently been used for a directly compressed tablet matrix.[24]

Carbamazepine (CZ) is an antiepileptic drug which shows variable absorption and variable bioavailability due to poor solubility. It is recommended to be administered in sustained release dosage form to improve patient compliance and to perform constant blood level with minimum side effects. Crystalline properties and bioequivalency of carbamazepine in sustained release hydrophilic matrix tablets using HPMC as swellable polymer, were studied.[25,26] It is known that Tragacanth mucilage is used as a diluent for a mixture containing carbamazepine.[27] Problems may be encountered with CZ tablets prepared by wet granulation if the granules are not thoroughly dried before processing, such as rehydration and recrystallisation of the drug throughout the tablet which may affect disintegration properties and possibly absorption.[28] Whereas, the direct compression is obviously the most convenient technique for tablet manufacture as it provides increased product stability, considerable cost reduction and reduced processing time.[29]

Therefore, the present study deals with the

application of direct compression technique to prepare sustained release carbamazepine matrix tablets. Different levels (0 to 25 %w/w) of Eudragit RS 100 and Tragacanth were tested to select the best level of matrix forming material that provides the most release prolonging effect, by direct compression technique using Avicel PH 102 and anhydrous lactose as directly compressible vehicles. Examination of the release characteristics of the drug from the directly compressed tablets as well as the determination of the release mechanism were also carried out.

MATERIALS AND METHODS

Materials

Carbamazepine; Gift from DAR-AL DAWA Co Jordan. Eudragit RS 100; Rohm Pharma, Germany. Tragacanth; JC, UK. Anhydrous Lactose and Avicel PH 102; Janssen Chemica, Belgium. Talc; T.S.S.N.E (Chemicals), Jordan. Tegretol®; Ciba products, Novartis Pharma, Basel, Switzerland.The other ingredients used are of pharmaceutical analytical grade.

Methods

Preparation of matrix tablets

Ten formulations of matrix tablets of carbamazepine (CZ) were prepared by direct compression, in addition to the control formula. The composition of these formulations are shown in Table I. Tragacanth and Eudragit RS 100 were used as natural polymer and synthetic polymer, respectively, at concentrations of 3.125%, 6.25%, 12.5%, 18.75%, and 25 %w/w. Microcrystalline cellulose (Avicel PH 102) and anhydrous lactose were used as directly compressible diluents, and talc as a lubricant. The ingredients were thoroughly mixed in a cubic mixer (Erweka, Germany) for 10 min and passed through 250 μm mesh screen. The matrices were made by direct compression of the mixture in a Korsch tablet machine (EKO, Germany) equipped with a 8-mm flat-face punches. Target tablet weight was 0.200 g.

The flow properties of powders of each ingredient and each mixture before compression was determined by applying the bulk density measurements, then the Hausner factor and Carr index values were calculated.[30]

Evaluation of tablets

Uniformity of weight

Twenty tablets were taken randomly and weighed individually, and tested according to the USP/NF (1995) test. The average weight, the standard deviation and the coefficient of variation percent (C.V.%) were calculated.

Uniformity of diameter and thickness

The diameter and thickness of twenty tablets were determined individually using Erweka Hardness Tester TBH_{30}, with thickness attachment, Germany. Also, the average and C.V.% was calculated.

Table I: Composition of carbamazepine tablets formulations.

Symbol / Materials (mg)	E1	E2	E3	E4	E5	T1	T2	T3	T4	T5
Carbamzepine	100	100	100	100	100	100	100	100	100	100
Eudragit RS 100	50	37.5	25	12.5	6.25	-	-	-	-	-
Tragacanth	-	-	-	-	-	50	37.5	25	12.5	6.25
Anh. Lcatose	-	12.5	25	37.5	43.75	-	12.5	25	37.5	43.75
Avicel PH 102	48	48	48	48	48	48	48	48	48	48
Talc	2	2	2	2	2	2	2	2	2	2

Tensile Strength

The tensile strength (Ts) was calculated from the equation:

$$Ts = 2H/\pi TD \quad \ldots\ldots \quad (1)$$

where T is the thickness, D is the diameter, and H is the hardness of tablets. These parameters were determined using Erweka TBH_{30} hardness tester. The average of hardness of 10 tablets and the C.V.% were calculated.

Friability

The percentage weight loss was determined after rotation of twenty pre-weighed tablets for 4 min at 25 rpm using an Erweka Friabilator TAR_{20}, Germany.

Disintegration time

The average of time required for the disintegration of 6 tablets was determined using Pharma Test, (Italy) apparatus.

Dissolution studies

A USP/NF 23 Hanson dissolution apparatus with six baskets was employed for the dissolution study. One tablet was placed in each basket, rotating at 100 rpm in 900 ml of the dissolution medium (either 0.I N HCl of pH 1.2, or phosphate buffer of pH 6.8). The temperature was adjusted to be $37° \pm 0.5$ allover the tests. The experiment was run for 8 hours, during which samples were withdrawn at suitable time intervals, and replaced by equal volumes of dissolution medium kept at 37°. Samples were assayed spectrophotometrically, after appropriate dilution, at 284 nm for carbamazepine.

RESULTS AND DISCUSSION

Physical properties of crabamazepine tablets

The Hausner factor and Carr index values are presented in Tables (II and III) for individual ingredients and their mixtures before compression into matrix tablets. The bulk density of a powder is dependent on particle packing and changes as the powder consolidates. The case with which a powder consolidates can be used as an indirect method of quantifying powder flow. Hausner found that the ratio $D_f/D°$ (D_f is tapped bulk density and D° is fluff bulk density) was related to interparticle friction and could be used to predict powder flow properties.[30] Hausner showed that powder with low interparticle friction had ratios of approximately 1.2, where more cohesive, less free-flowing powders such as flakes have Hausner ratios greater than 1.6. Carbamazepine powder showed poor flowability as indicated from value of Hausner factor (1.4) and Carr's index value (28.86), while the other four ingredients (Avicel PH 102, anhydrous Lactose, TG, and ERS 100) showed good flowability as appeared from low value of Huasner factor (less than 1.2) and low value of Carr's index (8.55-13.28). Carr was developed another method of measuring powder flow from bulk densities.[30] According to Carr there is a relationship between descriptions of powder flow and % compressibility like; range 5-15 is excellent flow, range 12-16 is good flow, and range 23-35 is poor flow. Nevertheless, the control formula of carbamazepine (S), without swellable polymers, showed acceptable flowability (Hausner factor= 1.23 and Carr index = 18.41) Table III. This means that the flowability of carbamazepine powder was improved by mixing with directly compressible vehicles; Avicel PH 102 and anhydrous lactose. The mixtures of carbamazepine tablets containing TG exhibited better flowability than ERS 100, because the former powder has low values of both Hausner factor and Carr index than the later as shown in Table II. Thus, TG increment improved the flowability more than ERS 100 did.

Table II: The flow properties of the materials used.

Material	Hausner's factor	Carr's index
Carbamazepine	1.41	28.86
Avicel PH 102	1.10	9.01
Anh. Lactose	1.15	13.28
Tragacanth	1.09	8.55
Eudragit RS 100	1.12	11.05

Table III: The flow properties of the materials mixtures before compression into matrix tablets.

Formula symbol	Polymer content %w/w	Hausner's factor	Carr's index
E1	25.00 Eudragit	1.38	27.27
E2	18.75 Eudragit	1.38	27.27
E3	12.50 Eudragit	1.39	28.28
E4	6.25 Eudragit	1.35	26.04
E5	3.125 Eudragit	1.27	21.11
T1	25.00 TG	1.24	19.32
T2	18.75 TG	1.25	20.00
T3	12.50 TG	1.29	22.47
T4	6.25 TG	1.28	21.59
T5	3.125 TG	1.32	24.16
S Control (CZ)	0	1.23	18.41

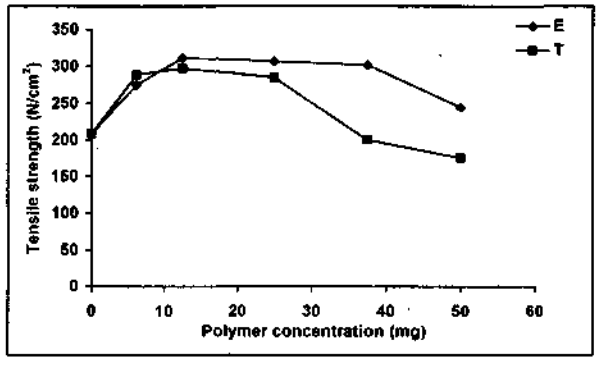

Fig. 1: Effect of swellable polymer concentration on the tensile strength of the prepared tablets.

Table IV represents the physical properties of the prepared carbamazepine matrix tablets. All the batches of tablets showed good uniformity of weight, diameter and thickness with acceptable friability values according to the USP/NF 23 requirements. As shown in Table IV and Fig. 1, by increasing ERS 100 content, an increase in the tensile strength of carbamazepine tablets was obtained. An increase of tensile strength of matrix tablets was also observed by increasing their content of TG up to 12.5 %w/w, but at higher content of TG (18.75, and 25 %w/w), the tensile strength start to decrease relatively. Involvement of ERS 100 improved the mechanical strength of carbamazepine matrix tablets more than TG, and generally, the two polymers improved the mechanical properties of matrix tablets as compared to the formula of carbamazepine tablets (S) without polymers.

Carbamazepine matrix tablets contain 3.125 %w/w of either ERS 100 or TG and 6.25 %w/w of ERS 100 showed disintegration time of 10.25, 30.36, and 31.24 minutes, respectively. While matrix tablets containing higher percentage of polymers (formulas E1, E2, E3 and T1, T2, T3) as shown in Table IV gave longer disintegration time than two hours, which is desirable in sustained release dosage form. The shorter disintegration time of matrix tablets of low content polymers was attributed to their swelling properties produce stress inside the tablets causing their disintegration rapidly, but at higher concentrations their swelling produce gelling network around the tablets preventing their disintegration.[11]

Release studies

The release rate of carbamazepine from the prepared matrix tablets was decreased by increasing ERS 100 or TG content in the tablets as seen in Figs 2-5. This could be due to the contribution of longer disintegration time of matrix tablets containing higher percentage of these polymers in this phenomena. The most sustaining effect could be obtained from tablets

Table IV: Physical properties of the prepared carbamazepine matrix tablets.

Parameter / Formula	Uniformity of diameter (nm)	Uniformity of thickness (mm)	Uniformity of weight (g)	Friabilitiy value Loss%	Disintegration time (min)	Tensile strength (N/cm^2)
E1	8.05 (0.614)	3.19 (1.998)	0.1971 (2.297)	0.577	> 120	244.19 (7.897)
E2	7.97 (0.072)	3.22 (1.740)	0.2002 (1.757)	0.260	> 120	301.90 (6.223)
E3	7.97 (0.321)	3.19 (2.681)	0.2021 (2.566)	0.297	> 120	306.44 (6.025)
E4	7.97 (0.335)	3.05 (1.920)	0.2016 (2.040)	0.373	31.24	311.39 (4.120)
E5	7.97 (0.351)	3.14 (1.371)	0.2032 (1.618)	0.331	10.25	275.27 (7.373)
T1	7.96 (0.192)	2.93 (0.521)	0.1900 (1.264)	1.069	> 120	175.51 (7.824)
T2	7.98 (0.618)	3.02 (3.457)	0.2026 (2.309)	1.034	> 120	199.97 (2.019)
T3	7.95 (0.214)	3.08 (2.333)	0.1999 (1.469)	0.259	> 120	284.43 (4.024)
T4	7.98 (0.179)	3.02 (5.963)	0.2042 (1.475)	0.345	75.02	297.18 (8.404)
T5	7.98 (0.165)	3.08 (1.347)	0.2020 (1.523)	0.269	30.36	288.03 (8.686)
S	7.97 (0.013)	2.93 (2.413)	0.2024 (3.769)	1.001	> 120	208.55 (13.87)

*Values between parenthesis means the coefficient of variation percent (C.V.%).

containing 25 %w/w of either ERS 100 or TG, followed by those containing 18.75 %w/w. Tablets containing 12.5 %w/w showed moderate release of the drug lied between the higher and lower content containing matrix tablets as observed from Figs 2-5.

No pronounced difference between release profiles of the drug in either acidic medium (0.1 N HCl, pH 1.2) or phosphate buffer medium (pH 6.8) from tablets containing ERS 100 (Figs 2 and 4), while those containing TG showed more sustaining effect in alkaline medium than in acidic medium (Figs 3 and 5). This might be attributed to the higher solubility of TG in acidic medium, whereas its viscosity was lost quickly,[27] while the solubility of ERS 100 is pH independent.[31]

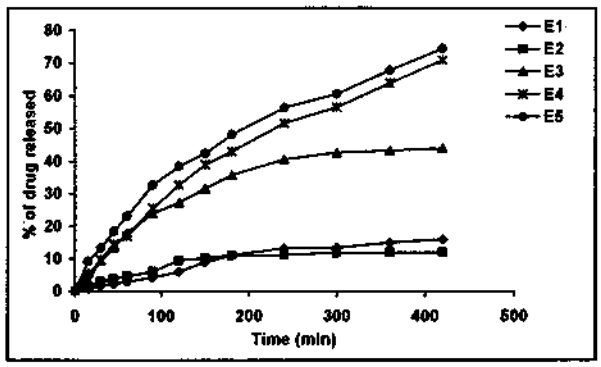

Fig. 2: Release profiles of carbamazepine matrix tablets containing Eudragit RS 100 in acidic medium (pH 1.2).

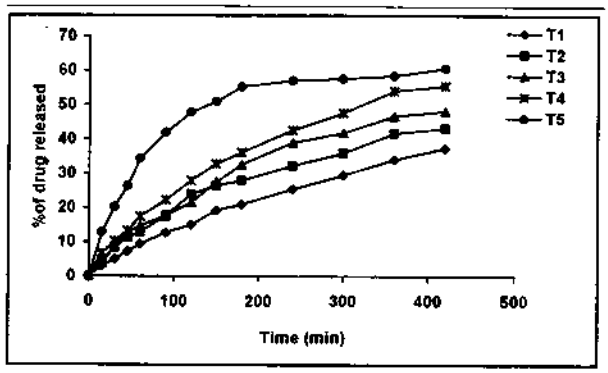

Fig. 3: Release profiles of carbamazepine matrix tablets containing Tragacanth in acidic medium (pH 1.2).

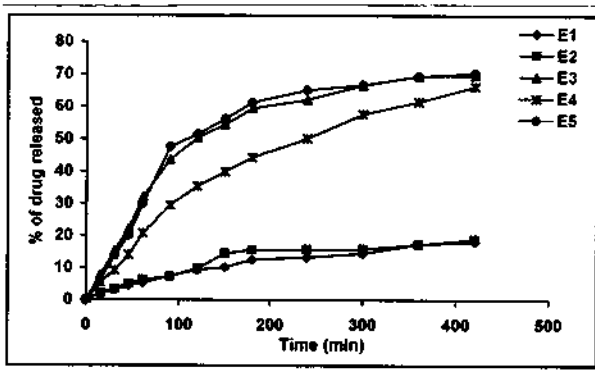

Fig. 4: Release profiles of carbamazepine matrix tablets containing Eudragit RS 100 in phosphate buffer (pH 6.8).

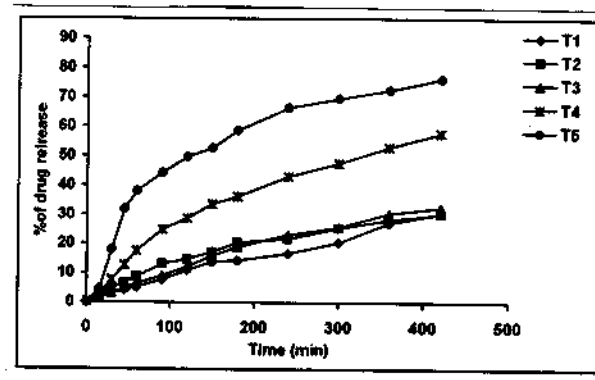

Fig. 5: Release profiles of carbamazepine matrix tablets containing Tragacanth in phosphate buffer (pH 6.8).

The release rate of Tegretol® commercial tablets was studied in comparison to that of matrix tablets containing 25 %w/w of either ERS 100 (E1) or TG (T1) and standard carbamazepine tablets (S), without polymer are shown in Figs 6-7. The release profile of Tegretol® in acidic medium was similar to that of formula T1 with no significant difference, while ERS 100 containing formula E1 showed more sustained release profile. On the other hand, the standard formula of carbamazepine tablets (S) showed faster dissolution profile than those containing polymers and Tegretol tablets. Thus, it could be concluded that carbamazepine tablets containing 25 %w/w of TG (T1) possessed sustained release properties similar to that of Tegretol® commercial tablets. Therefore, as Tragacanth mucilage is used as diluent for a mixture containing carbamazepine,[27] the solid powder of TG can be used in controlled release of carbamazepine, in promise of using thickening or binding agent tragacanth as matrix former material, beside the synthetic polymer Eudragit RS 100.

Kinetic studies

Korsmeyer[13] used the following simple equation to study the mechanism of drug release from polymeric matrix tablets.

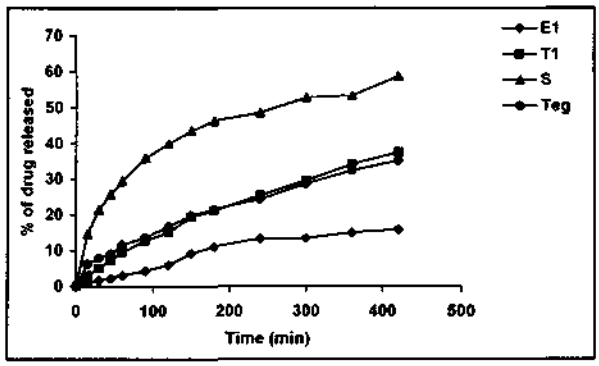

Fig. 6: Release profiles of carbamazepine matrix tablets containing 50 mg Eudragit (E1) or Tragacanth (T1) compared to Tegretol and standard carbamazepine tablets not containing swellable materials (S) in acidic medium (pH 1.2).

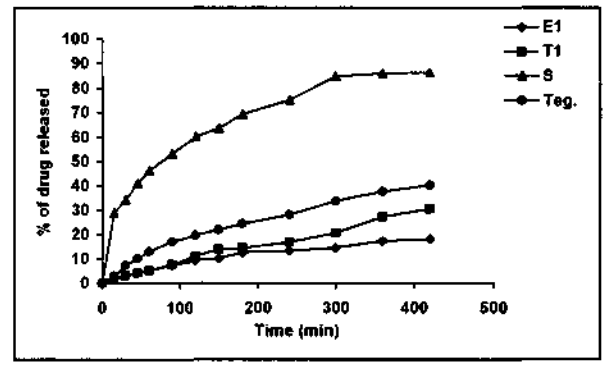

Fig. 7: Release profiles of carbamazepine matrix tablets containing 50 mg Eudragit (E1) or Tragacanth (T1) compared to Tegretol and standard carbamazepine tablets not containing swellable materials (S) in phosphate buffer (pH 6.8).

Table V: Release kinetics parameters of carbamazepine from different matrix tablets.

Formula	Acidic medium (pH 1.2)				Phosphate buffer (pH 6.8)			
	n	Log K	K	r	n	Log K	K	r
E1	0.9253	-1.1423	0.0721	0.9910	0.6674	-0.4607	0.3412	0.9956
E2	0.6415	-0.4813	0.3301	0.9670	0.6853	-0.4527	0.3526	0.9812
E3	0.6362	0.0708	1.1769	0.9806	0.6464	0.2646	1.8391	0.9598
E4	0.8400	-0.2874	0.5159	0.9861	0.7612	-0.1024	0.7900	0.9865
E5	0.6324	0.2330	1.7102	0.9950	0.7104	0.1239	1.3300	0.9505
T1	0.7642	-0.4089	0.3901	0.9985	0.8882	-0.8469	0.1423	0.9969
T2	0.6681	-0.0720	0.8472	0.9934	0.7332	-0.3885	0.4088	0.9923
T3	0.7316	-0.1784	0.6686	0.9899	0.9187	-0.8424	0.1438	0.9974
T4	0.6555	0.0624	1.1546	0.9979	0.8757	-0.4333	0.3687	0.9654
T5	0.4579	0.6614	4.5861	0.9618	0.6993	0.1700	1.4790	0.9120
S	0.3990	0.7448	5.5565	0.9898	0.3526	1.0353	10.848	0.9967
Tegretol®	0.5501	0.0930	1.2388	0.9940	0.7182	-0.2337	0.5839	0.9849

$$M_t / M\infty = Kt^n \quad \ldots\ldots \quad (2)$$

where $M_t / M\infty$ is the fraction of drug released at time "t", K is the kinetic constant incorporating structural and geometric characteristics, and n is the release exponent indicative of the drug release mechanism.

Ford[32] simplify and rewritten equation (2) as:

$$Q = Kt^n \quad \ldots\ldots\ldots \quad (3)$$

where: Q is the percentage of drug released at "t" time.

Thus the logarithmic form of equation (3) is:

$$\text{Log } Q = \text{Log } k + n \text{ Log } t \ldots \quad (4)$$

Table V shows the release kinetics parameters of carbamazepine from the prepared matrix tablets containing ERS 100 and TG. There is a goodness of fit analysis from plot of log Q against log t using equation (4), as appeared from the higher values of correlation coefficient (r = 0.93 - 0.999). As the diffusional exponent (n) value of drug release is more than 0.5 and less than 1.0 for all batches of matrix tablets, except two batches of T5 and S, this indicates the anomalous transport (non-Fickian diffusion release mechanism).[12] A combined diffusion and swelling /dissolution (erosion) might be responsible for this phenomena.[33]

CONCLUSION

Sustained release carbamazepine matrix tablets were successfully prepared using Eudragit RS 100 and Tragacanth as swellable polymers. The physical properties of all the prepared tablets were complied with USP/NF 23 requirements. In general the best formulas to obtain sustained release of carbamazepine were matrix tablets containing 18.75 or 25 %w/w of either Eudragit RS 100 or Tragacanth. The release rate of the formula (T1) containing 25 %w/w Tragacanth was similar to that of the commercial Tegretol® tablets. The mechanism of drug release of carbamazepine matrix tablets, showed anomalous (non-Fickian) diffusion release kinetics.

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