The Release of Diazepam from Different Conventional and Hollow Type Suppository Bases

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Abstract :

The objective of this study was to investigate the release profile of different fat and water soluble bases using diazepam as a model drug , and then to develop a satisfactory formula with a rapid release of diazepam from suppository bases .The study was conducted using theobroma oil ,glycerol-gelatin and glycerol-PEG1540 bases using conventional mold method for preparation .while the later base was utilized to incorporate diazepam (buffered solution) in a hollow type suppositories. The results indicated that all types of bases can be utilized to formulate diazepam as rectal suppositories with acceptable disintegration time (12, 10, 6, and 6min.), respectively . While 100% of the released drug had been shown different release profiles with different storage time (15, 30, and 45 days) in a refrigerator at 5°C , best results were obtained , when glycerol- PEG1540 used as a base for both conventional and hollow type mold methods .However , a decrease in the release rate of the drug was seen with glycerol-gelatin and glycerol-PEG1540 and to a lesser extent for glycerol-PEG1540 prepared by hollow type method .

Key words: Diazepam , Hollow type suppository

الخلاصة:

أن الهدف من هذه الدراسة هو للبحث عن شكل التحرر لعقار الدايازيبام كنموذج من خلال قواعد لبوسات شحمية و مائية , و من ثم تطوير تركيبة مقنعة بتحرر سريع لعقار الدايازيبام من قواعد هذه اللبوسات . ان الدراسة تواصلت باستعمال قواعد (زبدة الكاكاو , الكليسيرول-جيلاتين , الكليسيرول-بولي اثلين كلايكول١٥٤٠) و ذلك باستخدام طريقة الصب التقليدية بينما استعملت القاعدة الاخيرة لادخال الدايازيبام كسائل في تحاميل مجوفة . اشارت النتائج الى ان كل القواعد المستعملة من الممكن استخدامها لتركيب الدايا زيبيام كتحاميل شرجية باوقات اضمحلال (٦,٦,١٠,١٢) دقيقة على التوالي. بينما وجد ان نسبة ١٠٠% من العقار المتحرر من هذه القواعد باشكال مختلفة قد تأثر بفترات خزن ٤٥,٣٠,١٥ يوماً في درجة تبريد ٥ مئوية , كما ان افضل النتائج كانت عندما استعمل الكليسيرول-بولي اثلين كلايكول١٥٤٠ كقاعدة في كلا الطريقتين الصب و المجوفة . ومع ذلك فان نقصان في معدل سرعة تحرر العقار قد لوحظ في قاعدة , الكليسرول-جيلاتين و قاعدة الكليسيرول-بولي اثلين كلايكول١٥٤٠ و الى حد اقل في قاعدة الكليسيرول-بولي اثلين كلايكول١٥٤٠ بطريقة التجويف .

Introduction :

Suppositories are solid dosage forms of various weight and shapes ,intended to be use in the rectum, vagina or even in the urethra [(1)] , they disintegrate in the body cavity either by melting or by dissolution [(2)]. Rectal anxiolytic suppositories are indicated for patients with systemic sedative action [(3)], or to avoid hepatic first pass mechanism [(4)] , and also in post operative treatment [(5)] .Since most of sedative drugs are used widely , mainly diazepam [(6)], so it is of wise to use it as suppositories in children and elderly patients as sedative-hypnotic agent in the management of clinical conditions [(7, 8)] , However , rectal solution of diazepam has not been used widely , due to its ability to leak out of the rectum , and then no efficient drug treatment obtained .This study has conducted by incorporated diazepam as a powder in melted bases and as a buffered solution in an engraved cavity within backbone of solid suppository [(9)] , in addition to develop most effective rapid release of diazepam from drug solution rather than dispersed diazepam in a suppository bases [(10, 11)]

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Experimental

***Materials* :**

- Diazepam, supplied by Sammara"a Drug Industry "SDI ,256BN6/2004,
- Polyethylene glycol1540 ,BDH chemicals ,Ltd. ,Pool ,England.
- Disodium hydrogen orthophosphate , potassium dihydrogen orthophosphate , E.merk ,Darmstadt, Germany.
- Polyethylene sorbitan monolaurate (tween 20) , Evans , Liverpool , England .
- All other reagents were of analytical grade .

***Instruments* :**

- Balance , sartorious AG , Gottingen ,Germany .
- Dissolution apparatus , Copley , type , FH 16 – D , Nottingham , England .
- Disintegration apparatus , water bath , Kotterman ,Ollmann , and Co. ,KG , D-6360 , Friedberg – Germany .
- pH- meter , pH 211 , microprocessor , Italy .
- Suppository mold 1Gm. ,stainless steel , ERBO Prazision Forminbau , GMPHD-7470 , Albstadt , England .
- UV- Visible spectrophotometer , Cintra 5 , Double- beam spectrophotometer operation , manual GBC – England .

***Methods* :**

Preparation of Diazepam suppositories :

The fusion method was used to prepare the conventional suppositories (table 1.), by mixing 5 mg.equivalent weight of diazepam in each 1g. . suppository base. After calculation the displacement value , the bases were melted using a water bath with continous stirring until homogenous mixture was produced , the melted mixture then poured into the metal suppository mold , and then cooled in a refrigerator maintained at 5 °C This process was conducted for the formulas (1,2 and 3,) , while formula 4 was prepared by hollow-type method described by ,Watanabe , et al [12] , which summarized by melting the bases at 45 °C , then mixing water until homogenous dispersion results . The melted bases then poured into 1g. suppository mold equipped with a cylindrical tube in the center and allowed to stand for two hours at room temperature to solidify ,after that a construction of a hollow cavity in the solidified base , 0.5 ml. of buffered diazepam solution (prepared by mixing diazepam powder in 3% w/w tween 20 buffered in pH 7.8) was added to each cavity, the opening at the back part of the suppository was sealed with the same melted base , each suppository in all formulas contain an equivalent amount 5mg. of diazepam .

Table (1): Different prepared formulas suppositories with various methods

Formula (1)	bees wax 10% Theobroma oil 90%	(Displacement value 0.88 ,Conventional)
Formula (2)	Gelatin 10% Glycerin 70% Water 20%	(Displacement value 1.04 , Conventional)
Formula (3)	PEG1540 30% Glycerin 50% Water 20%	(Displacement value 0.98 , Conventional)
Formula (4)	PEG1540 30% Glycerin 50% Water 20%	(Displacement value ″not involved″ , Hollow type)

Evaluation of Physical Properties of Suppositories :

The prepared suppositories were evaluated for disintegration time according to the method described in British Pharmacopoeia BP (13), each determination was carried out in triplicate run.

In-Vitro Dissolution Study :

The dissolution rates of diazepam release from both conventional and hollow-type suppositories were carried out , a rotating basket dissolution apparatus was used at 50 rpm. maintained at constant temperature of 37°C. The medium used was 500ml. of orthophosphate buffer solution with pH 7.8, at time intervals 2,4,8,16,32,and 64 minutes , 5ml. of samples were withdrawn and the amount of diazepam was determined by UV-spectrophotometry at λmax. 232nm , using phosphate buffer as blank solution, the total percentage of drug released from the mean triplicate samples were estimated .

Results and Discussions :

The disintegration time for the prepared suppositories in the formulas 1 ,2 ,3 ,and 4 was 12±0.28 , 10±0.1 , 6±0.05 , and 6±0.11 minutes respectively , these results were found in consistent of BP and FDA requirement for disintegration time of rectal suppositories . Tables 2,3,4,5 and figure (1) . show the percentage of diazepam released from 4 different formulas of suppository bases and the method of preparation , At the first day of preparation , the results indicated that the release of diazepam from the conventional and

hollow - type suppositories is variable. Formula 1, 2 and 3 which they are prepared by conventional method revealed that the rate of diazepam release from insoluble theobroma oil is very slow compared with the rate diazepam released from hydrophilic base glycerol-gelatin and glycerol- PEG bases. The time for 50% drug release was more than 60 minutes from formula 1, compaired with 16 and 5 minutes for bases in formula 2, and 3 ,respectively .

These results may be referred to the physico-chemical properties of both drug and the base used [14] . Diazepam is highly lipid soluble , so its presence in low concentrations in theobroma oil base will have slow step of escaping out side the base vehicle [10] . The slow release of diazepam from fatty bases may be attributed to its high lipid solubility and their greater retention within the oily base , that can be candidate to be sustained release dosage form ,when larger dose (10 -15 mg.) diazepam was dispersed in the base [15] . On the other hand , the release of diazepam from glycerol-PEG bases showed significant difference (P< 0.05) and revealed to be faster than that incorporated in glycerol-gelatin base ,since the time for 100% of drug release were about 32 and more than 64 minutes, respectively . These results were in consistent with the results obtained from piroxicam released when gelatinous base was employed[16], since gelatinous consistency of glycerinated gelatin in a dispersed system may be formed and decrease the drug release from gelatinous barrier . Meanwhile , the modification of suppository shape (hollow-type) by incorporating the diazepam as 1%(w/v) buffered solution (formula 4), revealed that the drug release is significantly (P< 0.05) faster than other conventional type used with the same base (formula 3), since the time required for 100% drug release was 8 and 32 minutes , respectively . This result may be attributed to the concept that all the diazepam present in a buffered solution (pH7.8 ,formula 4) ,was available to be absorbed and this last about 6 minutes of disintegration time for suppository to be dissolved, compared with that diazepam powder dispersed in glycerol-PEG 1540 base [17] . The effect of storage period on the dissolution rate of diazepam was investigated at 5°C for 15 ,30 ,and 45 day ,the results were indicated that there is no significant difference (P> 0.05) in the drug release from theobroma oil base (Formula 1) , when stored for 45 days (fig.2) , since the over all drug released remain limited (25-35%) within the lipophyllic base [11]. On the other hand ,the effect of storage on the diazepam released from glycerol-gelatin base (fig.3) showed no significant decreasing in the amount of diazepam released. This behavior may be attributed to the tendency of free (OH) groups of glycerin to form hydrogen bonds with many functional groups located on amino acids moieties in gelatin , and this may form a cross-linking network that hinder the drug release [18] .This result was in agreement with the result obtained by Hanaee J. ,et .al , [18] .In addition ,the release of the drug from glycerol- PEG1540 base for conventional suppositories (Formula 3), showed that the time for 50% drug release was 4-8.5 minutes, besides to that, unusual hollow-type suppository filled with buffered liquid diazepam showed no effect on the drug released , after one month of storage [19] .The over all results of this study , revealed that diazepam can be formulated as a rectal suppository dosage form utilizing glycerol-PEG 1540 as a water soluble base, with best percent of drug release using solution of diazepam within hollow-type method of preparation ..

Table (2) : Effect of storage on the release of diazepam (5mg.) from conventional theobroma oil suppository base at 5 °C

Percent of drug released after extensive period of storage time(*) .				
Time (min)	**One day**	**15 day**	**30 Day**	**45 day**
0	0	0	0	0
2	6±0.2	6 ±0.3	6 ±0.17	3±0.26
4	9±0.17	8 ±0.17	6 ±0.34	6±0.10
8	14± 1.0	15 ±0.5	12 ±0.5	12±0.45
16	26±2.64	24 ±1.0	23±0.46	18±0.52
32	30±0.9	29±0.6	26±0.5	22±0.6
64	35±1.05	30 ±0.4	27±0.69	25±0.25

(*) Each value represents the mean SD(±) ,with n=3 samples, and P<0.05 (significant), with corresponding percent of drug release .

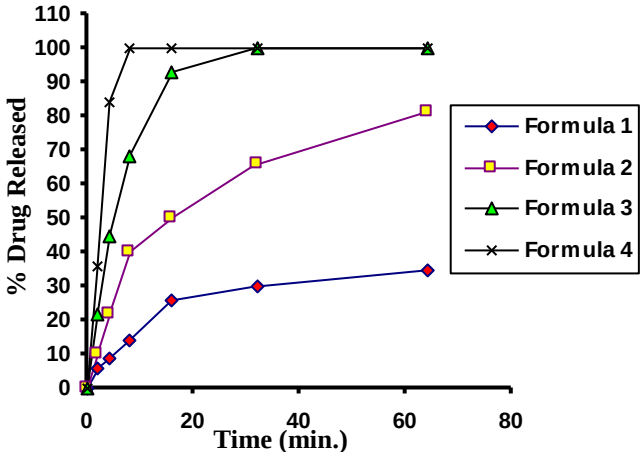

Figure 1. The percentage of diazepam released from different formulas (suppository bases) at first day of preparation in phosphate buffer pH7.8 at 37 °C .

Table (3) : Effect of storage on the release of diazepam (5mg.) from conventional glycerol-gelatin suppository base at 5 °C .

Percent of drug released after extensive period of storage time(*) .				
Time (min)	**One day**	**15 day**	**30 Day**	**45 day**
0	0	0	0	0
2	10±0.2	10±0.23	8±0.43	7±0.17
4	22±0.45	21±0.2	20±0.11	17±0.17
8	40±0.23	32±0.34	30±0.28	30±0.17
16	50±0.52	48±0.17	46±0.34	41±0.57
32	66±0.57	60±1.15	53±0.57	51±0.52
64	81±0.11	74±0.57	71±0.32	66±0.55

(*) Each value represents the mean SD(±) ,with n=3 samples, and P<0.05 (significant), with corresponding percent of drug release .

Table (4) :Effect of storage on the release of diazepam (5mg.) from conventional glycerol–PEG 1540 suppository base at 5 °C .

Percent of drug released after extensive period of storage time(*)				
Time (min)	**One day**	**15 day**	**30 Day**	**45 day**
0	0	0	0	0
2	22±0.28	20±0.46	18±0.34	17±0.34
4	45±0.28	40±0.57	38±0.05	32±0.05
8	68±0.57	66±0.51	60±0.11	56±0.52
16	93±0.55	90±1.1	82±0.42	77±0.46
32	100±0.0	100±0.0	88±0.40	85±0.48
64	100±0.0	100±0.0	100±0.0	100±0.0

(*) Each value represents the mean SD(±) ,with n=3 samples, and P<0.05 (significant), with corresponding percent of drug release .

Table (5) :Effect of storage on the release of diazepam (5 mg.) from hollow-type glycerol-PEG1540 suppository base 5 °C

Percent of drug released after extensive period of storage time(*) .				
Time (min)	**One day**	**15 day**	**30 Day**	**45 day**
0	0	0	0	0
2	36±0.46	26±0.57	22±0.34	20±1.15
4	84±0.23	68±1.12	50±0.55	42±0.51
8	100±0.0	90±0.56	80±0.51	72±0.52
16	100±0.0	100±0.0	100±0.0	96±0.48
32	100±0.0	100±0.0	100±0.0	100±0.0
64	100±0.0	100±0.0	100±0.0	100±0.0

(*) Each value represents the mean SD(±) ,with n=3 samples, and P<0.05 (significant), with corresponding percent of drug release .

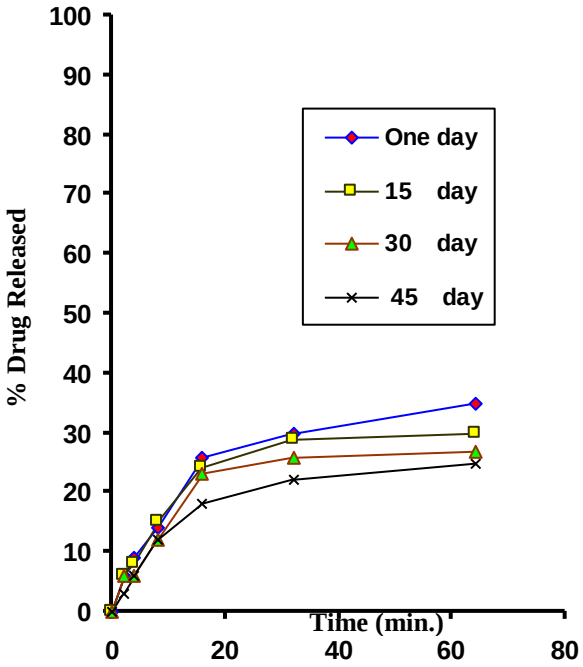

Figure 2. Effect of storage on the release of diazepam (5mg.) from conventional theobroma oil suppository base after different times in phosphate buffer pH7.8 at 37 °C .

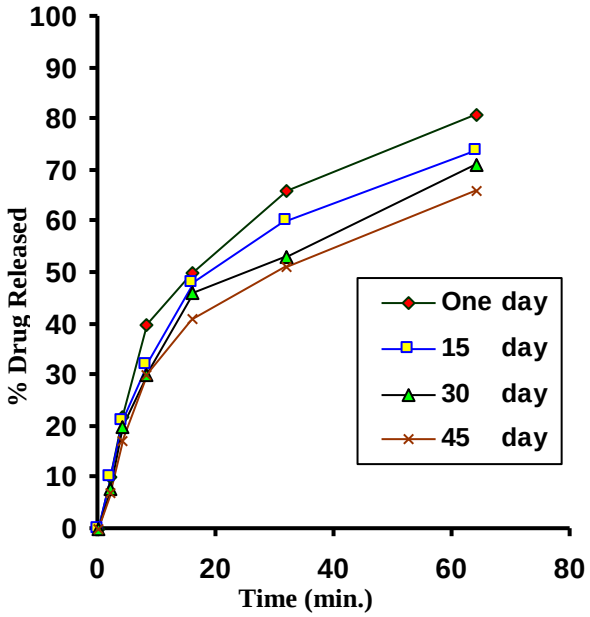

Figure 3. Effect of storage on the release of diazepam (5mg.) from glycero-gelatin conventional suppository base at different times in phosphate buffer pH 7.8 at 37 °C.

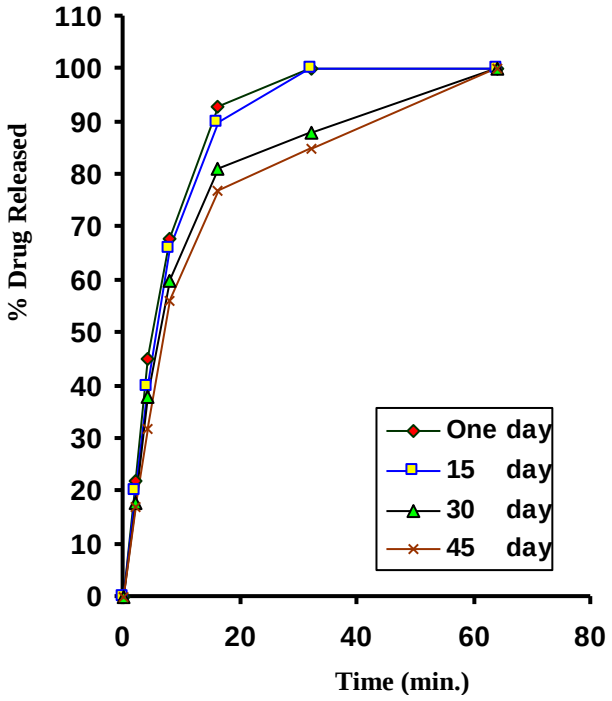

Figure 4. Effect of storage on the release of diazepam (5mg.) from conventional glycerol-PEG 1540 suppository base at different times in phosphate buffer pH 7.8 at 37 °C.

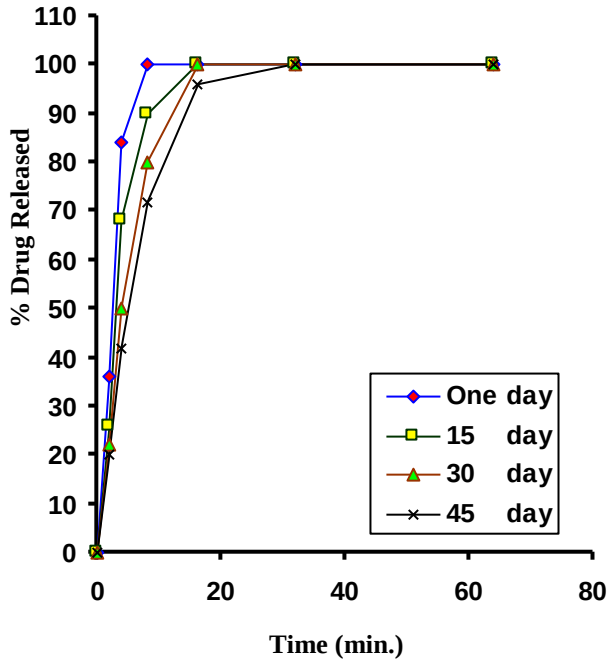

Figure 5. Effect of storage on the release of liquid diazepam (5mg.) from hollow-type glycerol-PEG1540 suppository base after different times in phosphate buffer pH 7.8 at 37 °C .

Conclusion :

Based on the results obtained from this study, one can conclude the followings :

1- Diazepam as an anxiolytic drug can be formulated successfully using different suppository bases.

2- Best results obtained , using glycerol-gelatin and glycerol- PEG1540 as a water soluble bases.

3- Hollow-type suppositories can be used, for fast drug release for another drug therapies .

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