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Swelling and Erosion Based Formulations for the Treatment of Chronic Seizures Using $(3)^2$ Factorial Design

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Abstract: The aim of present study was to prepare and optimize swelling and erosion based hydrophilic alginate matrix tablet for the treatment of chronic seizures. The matrix tablets were prepared by wet granulation technique using $(3)^2$ factorial design. In the preparation of matrix tablet, sodium alginate was used as matrix former and calcium chloride as cross-linking agent. To maintain proper tablet weight microcrystalline cellulose was used as filler. Swelling and erosion study was carried out in distilled water while *in vitro* dissolution study was carried out in 0.1N HCl for 2 h and further in phosphate buffer pH 6.8 for 8 h. The alginate-based matrix tablets swelled and/or eroded when come in contact with the aqueous medium and formed a continuous gel layer. The swelling of alginate based matrix tablets was depend upon rate of hydration in the media. Release study showed that drug release entirely depends upon swelling and erosion of matrix tablet and these determined the kinetics and mechanism of drug release. Release data in acidic media showed a good fit into Korsmeyer-Peppas equation but fitted well with zero-order release model, in neutral medium. It was concluded from the results that alginate based phenobarbitone tablets can be easily prepared for the treatment of chronic seizures in terms of controlled release of drug to obtain the effect over long time period.

Key words: Alginate · Matrix tablet · Swelling · Erosion · Drug release · $(3)^2$ Factorial design

INTRODUCTION

Natural polymers play an important role in the development of safe and effective drug delivery system. Alginate received much more attention for use in pharmaceutical dosage forms, especially as an excipient for controlled drug delivery system [1-5]. Alginates are a class of natural polymer synthesized by brown algae and seaweed. It is a linear unbranched polysaccharide, mainly containing different proportions of D-mannuronic acid and L-guluronic acid. These monomers are linked by glycosidic bonds [6-9]. The physical properties of alginates depend upon the composition and extent of the sequences and the molecular weight of alginates. The gel forming ability is mainly related to the proportion and arrangement of D-mannuronic to L-guluronic acid units present. Alginates are usually referred to as ''high M'' or ''high G'', depending on the proportions of these monomers respectively. Generally commercial product contains relatively higher proportion of D-mannuronic acid [7]. Alginates are also one of the important pH sensitive natural polymers, mainly contains free carboxylic acid in the polymeric chain, so can easily accept or release protons in response to environmental pH. Due to presence of carboxylate group, alginate can easily form salt with metal ions such as sodium ions, potassium ions and calcium ions [10]. Alginate salts are known to form a reticulated structure when in contact with calcium ions and this characteristic has been used to produce sustained release particulate systems for a variety of drugs, proteins and even cells [11, 12]. It was also shown in many studies that sodium salt of alginic acid (sodium alginate) is water soluble, while calcium salt of alginic acid (calcium alginate) is water insoluble [13]. Thus, in pharmaceutical formulations calcium alginate is mainly used to form matrix system. Glucoronic acid is the part of alginate that reacts with calcium ions to form insoluble salt. It is also concluded from many studies that with low levels of calcium, alginate forms temporary associations that gives rise to highly viscous, thixotropic solutions. At

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higher calcium levels, precipitation or gelation results from permanent associations of the chains [7]. The formation of a matrix upon hydration causes a gelatinous layer which can act as a drug diffusion barrier. A preferential use for alginate gel beads in the delivery of low solubility or macromolecular drugs has been suggested in many researches. Compressed hydrophilic matrices are commonly used in preparing oral prolonged release dosage forms. They are usually easy and economical to formulate [1, 14, 15]. Matrices incorporating alginate salts or a combination of alginate with other polymers have been employed to successfully prolong release of many drugs [1, 16, 17, 18]. Hydration of matrix form a viscous layer around the tablet, hydrated layer inhibit water penetration in to the matrix system, resulting in decrease in drug release over a long period of time [19]. Both water soluble an water insoluble drugs can be delivered using this type of hydrophilic matrix system. Release of water soluble drugs is mainly based on diffusion of drugs through the viscous hydrate layer while release of water insoluble drugs mainly based on erosion of matrix layer [20]. Strength of cross linking between alginate and calcium depends upon the concentration of both sodium alginate and calcium chloride. In present investigation water insoluble drug phenobarbitone is used as model drug. It comes under the category of barbiturates and mainly uses for the treatment of general-tonic-clonic seizures viz. status epilepticus. Epilepsy is a condition which requires a constant level of drug in blood over long period of time. To maintain this condition a matrix based system was formulated and studied in terms of drug release. The overall aim of present study is to investigate swelling, erosion and release behavior of sodium alginate-calcium chloride matrix in term of phenobarbitone release for the treatment of chronic seizures. Therefore a multilevel $(3)^2$factorial design approach was applied to study the effect of sodium alginate and calcium chloride concentration in the swelling and erosion behavior of matrix system.

MATERIALS AND METHODS

Materials: Phenobarbitone was obtained as a gift sample from Alchem Laboratories, Baddi India. Sodium alginate was procured from CDH Laboratory reagent, Central Drug House (P) Ltd, New Delhi, India. Calcium chloride and microcrystalline cellulose was purchased from Rankem Limited, New Delhi, India. All other materials were of pharmaceutical grade and used as supplied without further purification.

Table 1: Preparation of sodium alginate matrix tablet using $(3)^2$ factorial design

	Ingredients	
Formulation	Sodium alginate (X_1)	Calcium chloride (X_2)
F1	-1	-1
F2	0	-1
F3	+1	-1
F4	-1	0
F5	0	0
F6	+1	0
F7	-1	+1
F8	0	+1
F9	+1	+1

(Microcrystalline cellulose was used as filler to make tablet weight 150 mg)

X1: concentration of sodium alginate, Level:-1(15%), 0(20%), +1(25%)

X2: concentration of calcium chloride, Level:-1(15%), 0(20%), +1(25%)

Preparation of Alginate-based Matrix Tablets: In present research wet granulation technique was used to prepare matrix tablet. Drug dose was 50 mg decided for each tablet and added accordingly. According to table 1, all the ingredients were mixed physically for 25 min, using a mortar and pestle. Then appropriate amount of distilled water was added to prepare a wet mass. Wet mass was passed through 20 # sieve to prepare granules.

The granules were dried at 45°C for 24 h. Equivalent to 150 mg, granules were weighted and compressed by Cadmach punching machine (16 Station, Type: CMD3-16/MT, Cadmach Machinery Co. Pvt. Ltd. Ahmadabad, India)with 8 mm diameter flat faced tolling. Tablets were compressed at compression force of 2 N for 10 s [21].

Evaluation of Alginate-Calcium Chloride Matrix Tablets: Evaluation for weight variation: Twenty matrix tablets were randomly selected from each batches and evaluated for weight variation as per USP XXIV monograph. The results were expressed as mean values of 20 determinations [22-24].

Tablet Thickness Testing: The thickness of the matrix tablets was determined using vernier caliper (Mitutoyo Dial Thickness Gauge, Mitutoyo, Japan) and the results were expressed as mean values of 10 determinations, with standard deviations [22-24].

Evaluation for Tablet Hardness: Hardness of all batches was determined using Digital Force Gauge (Model:EL=500N, Electrolab). The test was carried out in triplicate for all batches as per USP XXIV monograph for

uncoated tablets. The tablet hardness was expressed in Newton (N) unit and mean and standard deviation of the tablet hardness were calculated [22-24].

Friability Measurement: Tablets of all batches were used to evaluate friability as per USP XXIV monograph. Friability testing was done by Roche friabilator with triplicate readings. The mean value of friability was calculated with standard deviation [22-24].

Disintegration Time: The standard USP test with discs was employed to assess the disintegration times, using disintegration tester (Electrolab: ED-2L, Mumbai, India). Disintegration test was carried out using 800 ml of distilled water at 37±0.5°C. The disintegration time was defined as the time necessary for complete disintegration of the matrix tablets, until no solid residue remains or only a trace amount of soft residue remains on the screen. Readings were calculated in triplicate and mean were noted with standard deviation [22-24].

Swelling or Water Uptake Studies of Alginate Matrix Tablets: The rate of test medium uptake by the alginate-calcium chloride matrix was determined by equilibrium weight gain method similar to that reported by others [25]. Dried matrix tablet was accurately weighed (W_0), placed in the closed plastic containers with the mesh underneath the tablets, rotating at 150 rpm using environment shaker-incubator (Model ES-20, Biosan, Latvia), with the dissolution medium of distilled water, at 37 ± 0.5°C. After 2, 5, 10, 20, 60 and 120 min, each container was removed from the incubator, the tablet with the pre-weighed mesh was withdrawn from the medium and lightly blotted with tissue paper to remove excess test distilled water and then reweighed (W1) on an analytical balance. The experiment was performed in triplicate for each time point and fresh distilled water was used for each individual time point. The percentage increase in weight due to absorbed liquid or water uptake was calculated at each time point from the following equation [Equation1]:

$$\% \text{ weight change} = (W_1\text{-}W_0/\ W_0)*100 \quad (1)$$

Matrix Erosion Study of Tablets: Matrix erosion studies were performed by a method similar to those of Roy and Rohera [26]. After the swelling studies, the wet samples were then dried in an oven at 80°C for 24 h time period, followed by cooling in desiccator and finally weighed until constant weight was achieved (final dry weight, W_2). The experiment was performed in triplicate for each time point. The percent tablet erosion (ES) at different times was estimated from the following equation [Equation 2]:

$$ES = (W_0\text{-}W_2)/W_0*100 \quad (2)$$

After erosion, percentage weight remaining of the tablets was calculated from the following equation [Equation3]:

$$\% \text{ remaining} = 100\text{-}ES \quad (3)$$

Factorial Design: In present investigation two independent variables (concentration of sodium alginate and concentration of calcium chloride), at three levels (-1, 0 and +1) were selected to study, the effect of these variables on drug release (dependent variables); according to table 1. The complete design of this research was consisting 9 experiments. The response of experiment was measured as erosion of matrix tablet. Traditional pharmaceutical formulations are designed to change one variable at a time. This is a time consuming process and using this type of formulation design it is not easy to predict the combined effect of more than one variable. To avoid this type of problems some statistical tools such as factorial design can be used. Reduced equation having statistical significant value for $(3)^2$ factorial design was shown as following equation [Equation4]-

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad (4)$$

Where, Y is the response of variables (dependent variable), b_0 arithmetic mean response of nine batches and b_1 estimated coefficient for factor X_1. The coefficients corresponding linear effects (*b*1 and *b*2), interaction (*b*12) and the quadratic effects (*b*11and *b*22) were determined from the results of the experiment. Deviation from predicted response was calculated using following equation [Equation5]

$$\% \text{ deviation} = \{(\text{predicted response-experimental response}) / \text{predicted response}\} * 100 \quad (5)$$

Drug Content: The tablets were powdered and 50 mg equivalent weight of phenobarbitone in tablet powder was accurately weighed and transferred into a 100 ml volumetric flask. Initially, 10 ml of phosphate buffer (pH6.8) was added and shaken for 10 min. Then, the volume was made up to 100 ml with buffer. Subsequently, the solution in volumetric flask was filtered and 1 ml of the filtrate was diluted and analyzed at 241 nm using UV-visible spectrophotometer (Shimadzu UV-2450, Japan).

The drug content of the each sample was calculated from standard curve.

***In vitro* Release Studies:** To examine the effects of sodium alginate and calcium chloride concentration on drug release, USP dissolution apparatus equipped with baskets which was operated at 50 rpm. 900 ml of 1.2 N HCl (pH1.2) was used as dissolution media at 37±0.5°C for 2 h. Dissolution of same tablets was further carried out in phosphate buffer pH6.8 for 8 h. The amount of drug released was measured at the suitable time interval and was then determined spectrophotometrically (UV-visible spectrophotometer, Shimadzu UV-2450, Japan) in a 1 cm cell at 241nm. Each *in vitro* release study was performed in triplicate and mean value was calculated with standard deviation.

Analysis of Drug Release: The mechanism of drug release from alginate-based matrix tablets during dissolution tests in 0.1 N HCl and phosphate buffer pH 6.8 was determined using zero-order, first-order and Higuchi equation. All of these models failed to explain the drug release from alginate matrix tablet. Therefore, these dissolution data's were fitted to Korsmeyer-Peppas equation [Equation 6], which is often used to describe the drug release behavior from polymeric systems when the mechanism is not well-known or when more than one type of release phenomena is involved [27,28].

$$M_t/M_f = k.t^n \quad (6)$$

where M_t/M_f is the drug released fraction at time t, k is a constant incorporating the structural and geometric characteristics of the matrix tablets, n is the release exponent, indicative of the drug release mechanism. When determining the n exponent, only the portions of the release profile where $M_t/M_f = 0.6$ were employed. To clarify the release exponent for different batches of matrices, the log value of percentage drug released were plotted against log time for each batch according to the following equation [Equation 7]:

$$\log [M_t/M_f] = \log k + n \log t \quad (7)$$

In case of Fickian release (diffusion), the n has the limiting values of 0.45 for release. Case II transport or relaxation controlled delivery; the exponent n is 0.89 for release. The non-Fickian release or anomalous transport of drug occurred when the n values are between the limiting values of Fickian and Case II transport. The non-Fickian kinetics corresponds to coupled diffusion/polymer relaxation. Occasionally, values of $n > 0.89$ for release from cylinders have been observed, which has been regarded as Super case II kinetics. This mechanism could result from an increased plasticization at the relaxing boundary (gel layer around the matrix).

RESULT AND DISCUSSION

Physical Characterization of Sodium Alginate-Calcium Chloride Matrix Tablets: As per the Table 2, the formulated matrix tablets met the Pharmacopoeial requirement of uniformity of weight. All the batches confirmed to the requirement of assay, as per USP. Hardness, percentage friability and thickness were all within acceptable limits.

Study showed that percent weight variation was observed between 0.02 to 2.73 %, which was well within the acceptable limit for uncoated tablets as per United States Pharmacopoeia. Since mechanical strength is of paramount importance in successful formulation hence, the hardness of tablets was determined and was found to be in the range of 20.1 N to 21.3 N. Friability was observed between 0.42 to 0.99 %, which were below 1% indicating

Table 2: Physical properties of matrix tablet*

Formulation	Weight variation (%) n=20	Thickness (mm) n=10	Hardness (Newton) n=10	Friability n=5	Disintegration time(s) n=3	Drug content (mg) n=3
F1	0.26±0.09	1.69±0.03	20.1±0.39	0.56±0.05	78.14±3.8	49.1±0.03
F2	2.73±0.36	1.63±0.20	20.3±0.96	0.72±0.08	105.29±14.1	47.7±0.09
F3	0.14±0.27	1.71±0.05	21.3±0.48	0.64±0.13	39.87±2.9	49.2±0.06
F4	0.62±0.31	1.72±0.19	20.3±1.23	0.97±0.06	48.56±5.7	48.6±0.06
F5	0.02±0.07	1.68±0.07	20.8±0.81	0.99±0.05	61.59±3.3	49.2±0.03
F6	0.43±0.28	1.64±0.18	21.3±0.67	0.67±0.07	18.92±7.8	48.9 ±0.07
F7	0.84±0.30	1.72±0.16	20.7±1.54	0.48±0.07	37.17±8.7	47.6±0.13
F8	0.98±0.59	1.70 ±0.04	20.6±0.33	0.88±0.09	39.99±3.3	49.0±0.01
F9	0.13±0.07	1.70± 0.03	21.0±1.17	0.42±0.08	48.87±(6.7)	47.8±0.07

*values in parenthesis represent standard deviation

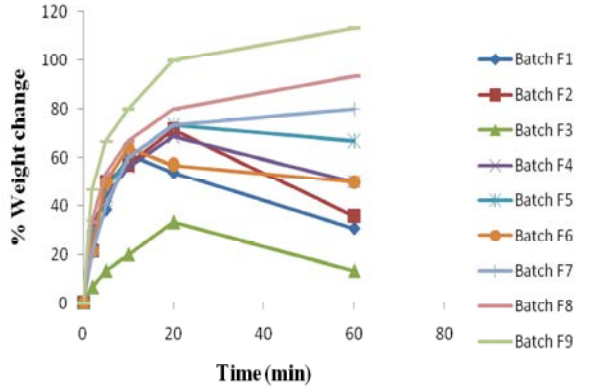

Fig. 1: Observation graph between % weight change and time

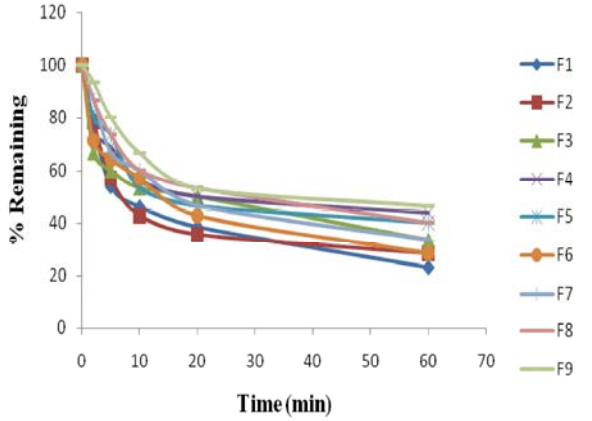

Fig. 2: Observation graph between % matrix remaining and time for alginate based matrix tablet

sufficient mechanical integrity and strength of the prepared tablets. The two study viz. hardness and friability indicates good mechanical strength of tablets, so ease of handling during transportation and storage. Thickness of tablets was also measured to evaluate efficiency of process development. Thickness of tablet was found in between 1.63 to 1.72 mm. Almost uniform thickness of tablets showed that this process is efficient to produce matrix based tablet.

Swelling and Erosion Behavior of Alginate-Calcium Chloride Matrix Tablet: Swelling and erosion study were carried out for all batches in distilled water. The results of these tests are provided as the percentage weight change (Figure 1) and percentage remaining (Figure 2) of initial tablet mass.

The swelling behavior is the indication of the rate at which tablet absorbed water from dissolution media and swelled. Visual observation of swelling study indicated that the matrices appeared to swell almost from

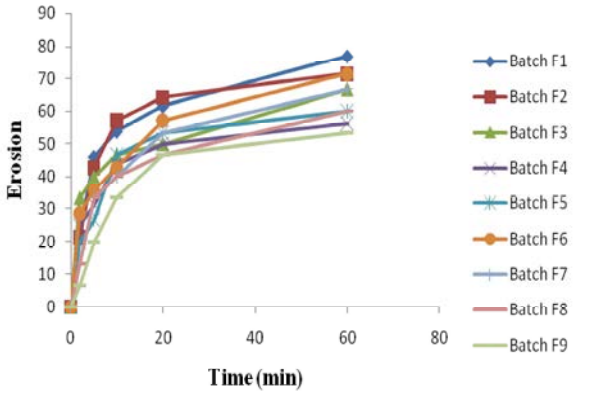

Fig. 3: Observation graph for erosion of alginate based matrix tablet

the beginning and a viscous gel mass was created when they came into contact with the medium. Hydration of matrix layer results in the formation of gel structure around the tablet matrix. Up to certain limit this gel structure retards the penetration of water in to the core matrix. The changes in tablet weight, characteristic of water uptake and swelling, started from the beginning of the study and continued until 60 min of experiment. The percentage remaining of the matrices reflects the amount of polymer that is dissolved in the media and the erosion of tablet matrix in different media during the dissolution process. Weight loss from the tablets increased progressively with the swelling time because tablet contact time with water increased. The extent of erosion in media also increased progressively, as the percentage remaining of tablet mass decreased, with the increased swelling time.

Matrix erosion indicated the weight loss from matrix tablets immersed in dissolution media as a function of time. Calcium ions can react with sodium alginate, to cross-link the polymer through the carboxylate and modify rheological properties and gel layer integrity. As a result, there may be an impact on release properties. In fact the ionic interactions between G blocks of alginate and calcium ions determine the formation of a cross-linked gel. Adding a lower amount of calcium chloride, in the formulation seemed not to influence the swelling and erosion of matrix tablets An optimum concentration of calcium chloride is always required to react with optimum concentration of sodium alginate (water soluble) to form calcium alginate (relatively very less water soluble). Sodium salt of alginic acid is relatively more water soluble than the sodium salt and this is basic reason to select calcium chloride-sodium alginate matrix for the formulation of phenobarbitone tablet.

Table 3: Predicted and experimental responses obtained from studied parameters

	Formulations								
Erosion (%)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Predicted response	70.08	67.23	69.53	59.22	62.10	68.56	63.01	63.03	57.48
Experimental response	76.92	71.43	66.67	56.25	60.00	71.43	66.67	60.00	53.33
Deviation (%)	-9.8	-6.3	4.1	5.0	3.4	-4.2	-5.5	4.8	7.2

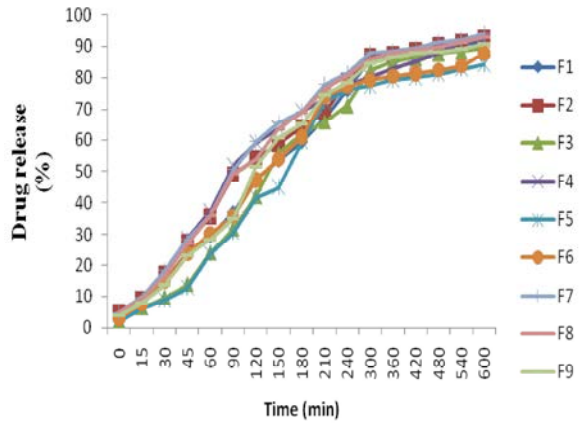

Fig. 4: Release profile of phenobarbitone from alginate based matrix tablets

Close resemblance was observed between predicted and experimental value of erosion. The obtained data of erosion indicate the significant role of interaction between two independent variables in controlling the erosion of matrix. To assess the reliability of this model, a comparison between the experimental and predicted values of the responses is also presented in Table 3.

Release Behavior of Phenobarbitone from Sodium Alginate-Calcium Chloride Matrix Tablets: Figure 4 shows the *in vitro* release profile of phenobarbitone from alginate based matrix tablet. Release study was carried out in 1.2N HCl (pH 1.2) for 2 h and subsequently in phosphate buffer pH6.8 for 8 h.

It is also concluded from the release data that drug release from the matrix depend upon the pH of medium. Although the matrices generally showed a higher ability to swell in neutral medium than in acidic medium, therefore the drug release in neutral medium, from high M alginate tablets, was faster than in acidic medium. It is perhaps reasonable to expect faster release in neutral medium than acidic medium as the alginate is more soluble at higher pH.

Table 4: Korsmeyer-Peppas model fitting of release data[a]

	Korsmeyer-Peppas model			
Batch	Correlation coefficient, r^2	Kinetic constant, k	Diffusion exponent, n	Order of release
In 0.1 N HCl (pH 1.2)				
F1	0.9848	0.008	0.98	Super class II
F2	0.9779	0.013	0.89	Super class II
F3	0.9899	0.011	0.88	Super class II
F4	0.9688	0.009	1.02	Super class II
F5	0.9869	0.009	0.78	Super class II
F6	1.0301	0.012	0.89	Super class II
F7	1.1010	0.008	1.03	Super class II
F8	0.9799	0.014	1.09	Super class II
F9	1.0211	0.008	0.79	Super class II
In pH 6.8 phosphate buffer				
F1	0.9783	0.010	0.89	Non-Fickian
F2	1.1021	0.009	0.81	Non-Fickian
F3	0.9782	0.012	0.92	Non-Fickian
F4	0.9687	0.011	0.97	Non-Fickian
F5	0.9788	0.013	0.86	Non-Fickian
F6	1.0260	0.009	0.88	Non-Fickian
F7	0.9883	0.008	0.95	Non-Fickian
F8	0.9769	0.009	0.90	Non-Fickian
F9	0.9856	0.011	0.98	Non-Fickian

[a] Analyzed by the regression coefficient method.

Erosion of matrix tablet in neutral pH was higher at compared to low pH, this results in more drug release in neutral pH as compared to acidic pH. It is also shown in many studies that calcium salts of alginate could be replaced by protons in acidic medium to form alginic acid which stimulated the tablet disintegration. Alginic acid is water insoluble polymer, swells in water and has been used traditionally as a tablet disintegrant.

Analysis of Release Data: The drug release data were fitted to the Korsmeyer-Peppas equation. The mechanism of drug release from matrices containing swellable polymers is complex and not completely understood. Some systems may be classified as either purely diffusion or erosion controlled, while most of them exhibit a combination of both mechanisms. In present study, the phenobarbitone release, in acidic medium, from alginate matrix tablets showed a good fit into the Korsmeyer-Peppas equation, indicating combined effect of diffusion and erosion mechanisms for drug release. As illustrated in Table 4 release data fit well with this model, as a correlation coefficient (r^2) greater than 0.9848 was obtained in all cases in acidic medium. The matrix tablets exhibited an anomalous (non-Fickian) diffusion controlled release in acidic medium. In neutral medium, on the other hand, drug release data of matrix tablets did not show a good fit into Korsmeyer-Peppas equation. Interestingly, most of the release data of matrix tablet formulations fitted well with super class II release model with a correlation coefficient (r^2) greater than 0.9688 (Table4). This is probably due to the extensive swelling of matrix tablets in neutral medium. These results were predicted in studies done before. It establishes a correlation among the swelling, erosion and drug release in matrices formulate with xanthan, karaya and locust bean gum.

CONCLUSION

It is concluded from the results that alginate based matrix tablet can be easily prepared by blending drug with sodium alginate and microcrystalline cellulose and then fabricating the tablets. Drug release from matrix tablet depends upon pH of the dissolution media. The matrix tablets swell and erode when come into the contact of media. The extent of matrix swelling, erosion and drug release determined the kinetics as well as mechanism of drug release from alginate-calcium chloride matrix tablets. Most of the release data in acidic medium showed a good fit into Korsmeyer-Peppas equation (indicating combined effect of diffusion and erosion mechanisms for drug release) but fitted well with zero-order release model, in neutral medium. The results of this study show that sodium alginate-calcium chloride based matrix tablets are able to provide sustained/ controlled release of phenobarbitone for the treatment of chronic seizures.

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