ISSN: 2515-8260 Volume 09, Issue 08, 2022

[Original Research Paper]

Design and Characterization of Fast Disintegrating Film for Phenobarbital

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Abstract

Epileptic seizures often cause transient impairment of consciousness, leaving the individual at risk of bodily harm. Therapy is symptomatic to which available drugs inhibit seizures. Phenobarbital exerts maximal antiseizure action at doses below those required for hypnosis. Phenobarbital is slowly absorbed from oral route, onset of action occurs within 30-60 mins, duration of action persist for 12-16 hours, 20-45% bound to plasma protein and only partly metabolized in the liver. Mouth dissolving films of phenobarbital can be used for emergency treatment of status epilepticus (SE) in all class of patients without need of trained persons. In the present work, an approach to develop and evaluate quick disintegrating films of Phenobarbital. Suitable film formers and plasticizers were selected based on optimization studies. Effect of superdisintegrants in formulation of mouth dissolving films at different concentrations has been investigated. Films were prepared by solvent casting method. The prepared films were evaluated for physicochemical parameters, *in vitro* disintegration & dissolution time, *in vitro* release rate study and stability study. The best formulation was found to be F3 showing 96.57 % drug release in 14 min, following first order kinetics. X-Ray diffraction studies show change in crystalline nature of drug in formulation.

Keywords: Mouth disintegrating film, phenobarbital, sodium starch glycolate, X-ray diffraction.

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Introduction

Of various solid dosage forms now a days the mouth dissolving products (tablets and films) have gained immense interest for drug delivery. [1] But the major drawbacks of mouth dissolving tablets are fear of swallowing, chewing, or choking. As they are more friable or fragile, they require special and expensive packaging, special transportation and storing conditions. These above drawbacks of mouth dissolving tablets are eliminated by approaching new method as quick disintegrating films or mouth dissolving films. [2].

Mouth dissolving films have become popular as a new drug delivery system because they are easy to administer and exhibit quick onset of action. As indicated earlier, a need exists for a fast-dissolving delivery system with the aforementioned capabilities for use within the pediatric and geriatric populations [3-7].

Epileptic seizures often cause transient impairment of consciousness, leaving the individual at risk of bodily harm and often interfering with education and employment. Therapy is symptomatic to which available drugs inhibit seizures, but neither effective prophylaxis nor cure is available. Compliance with medication is a major problem because of the need for long-term therapy together with unwanted effects of many drugs. [8] Status epilepticus (SE) is recurrent epileptic seizure activity lacking full recovery of neurologic function between seizures, or continuous clinical and/or electrical seizure activity that lasts 30 min or longer, whether or not consciousness is impaired. [9-11]

Barbiturates are employed in the long term treatment of convulsions. Phenobarbital was the first effective organic antiseizure agent. Phenobarbital exerts maximal antiseizure action at doses below those required for hypnosis. Phenobarbital is very slightly soluble in water, completely but slowly absorbed from oral route, onset of action occurs within 30-60 min, duration of action persist for 12-16 h, 20-45% bound to plasma protein and only partly metabolized in the liver. [12-14]

Rapidly dissolving oral dosage form which can rapidly dissolve or disintegrate in the oral cavity has attracted a great deal of attention. [3, 15] Recently pharmaceutical industry has become increasingly aware of the need that pediatric and geriatric be considered as a separate and unique medicare population. Though geriatric and pediatric patients constitute a minor proportion of the population, its growth rate is high and hence will have significant impact on development of drug delivery systems. [16] Thus for pediatric patients who require long term treatment quick dissolving film of phenobarbital will be suitable drug delivery. In the present work, an approach to develop and evaluate quick dissolving films of phenobarbital for oral administration.

Materials and Methods

Material

All the materials used in the current study were of pharmacopoeial grade. Phenobarbital IP (Anglo-French Drugs and Industries Ltd. India). Methocel-E 15® and Methocel-E 50® NF (Dow Chemical Company, USA). Pectin LR and Pullulan JP (Lipoid GmbH, Germany). Sodium Starch Glycolate (Primojel®) Type- A (USP/NF) and Croscarmellose Sodium (Primellose®) USP/NF (DMV- Fonterra Excipients, Netherland). Hydroxypropyl cellulose LR, Gelatin LR and Xanthan Gum LR (S.D. Fine-Chem. Ltd.

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India). Glycerin LR (Ranbaxy Fine Chemicals Ltd., India). Propylene Glycol LR and Aspartame LR (S.D. Fine-Chem. Ltd., India).

Formulation mouth dissolving film of Phenobarbital

Fast dissolving films containing phenobarbital was fabricated by using solvent casting method. The films were formulated by using various grades of Hydroxypropylmethyl cellulose (HPMC) namely Methocel E15®, & Methocel E50® Premium LV as film former and sodium starch glycolate or croscarmellose sodium as superdisintegrants. The films were evaluated for following parameters. Compositions of phenobarbital mouth dissolving films are shown in Table 1.

Film Thickness

Thickness of films was measured using calibrated dial caliper (Mututoyo, Japan). [15]

Weight Variation

The study was carried out on 10 films obtained from each formulation batch. The mean weight of film as well as the deviation from the mean was calculated and recorded. [16]

Hydration Study

The film sample was weighed and placed on a stainless steel wire mesh. The wire mesh was then submerged in a petridish containing 20 ml distilled water. Increase in weight of the film was determined at regular time intervals until a constant weight was obtained. [1, 17]

Moisture Vapor Transmission

The percent moisture loss was determined by placing prepared film in desiccators containing anhydrous calcium chloride. After three d, the film was taken and reweighed. [18, 19]

Tensile Strength:

Film strip of dimension 5 X 2 cm^2 and free from air bubbles or physical imperfections was held between two clamps positioned at a distance of 3 cm apart. A cardboard was attached on the surface of the clamp via a double sided tape to prevent the film from being cut by the grooves of the clamp. During measurement, the strips were pulled at the bottom clamp by adding weights in pan till the film breaks. The force was measured when the films broke. [20]

Drug Content and Content Uniformity:

The drug content and content uniformity test was performed to ensure uniform and distribution of drug. 3 cm^2 films was cut, weighed and dissolved in 100 ml methanol. 3 ml of supernant aqueous was withdrawn and transferred in 100 ml volumetric flask. Final dilution up to mark was done using simulated saliva and analyzed UV –Vis spectrophotometrically (Shimadzu Corporation, Japan) at 254 nm wavelength. Content uniformity of phenobarbital films were done by selecting randomly five 3 cm^2 films from different batches and performing study same as drug content. [16]

***In vitro* Disintegration and Dissolution Time:**

The disintegration time is the time when a film starts to break or disintegrate. The dissolution time is the time when the film completely dissolves. The *in vitro* disintegration and dissolution time of fast-dissolving films was determined visually in a glass dish of 25 ml distilled water with swirling every 10 s. [15]

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***In vitro* Dissolution Study:**

The *in vitro* dissolution test was carried out in a *Ph. Eur. 4 ed.* paddle dissolution apparatus TDT-8 (Electrolab, India). Samples of Phenobarbital-loaded films equivalently containing 15 mg ($3cm^2$) was cut and placed in dissolution media. The dissolution medium consisted of 900 ml freshly deionized simulated saliva (pH 6.8), maintained at 37 ± 1 ^{0}C and stirred at 100 rpm. Samples of 1 ml were withdrawn at predetermined time intervals & replaced with fresh medium. The samples were filtered through whatman filter paper & phenobarbital concentrations were assayed UV–Vis spectrophotometrically (Shimadzu Corporation, Japan) at 254 nm after final appropriate dilution. The results were the average of three determinations. The dissolution profile of conventional marketed tablet luminal containing 15 gm equivalent phenobarbital was also determined using same experimental set-up. [15, 21]

Surface Morphology Study:

The surface morphology of formulated phenobarbital film was assessed using a scanning electron microscope SEM JSM -6380 (JEOL, Japan). Pictures were then taken at an excitation voltage of 15 Kv. [19]

X-Ray Diffraction study:

The X-Ray diffraction of phenobarbital, physical mixture, and optimized phenobarbital formulation was carried using X-Ray diffractometer (Philips analytical B.V., Netherland) with Cu–Kα radiation, collimated by 0.0080 divergence slit and 0.20 receiving slit and scanned at a rate of 2.40/ min over the 2θ range of 2-600. [22]

Stability Studies:

Stability tests are the series of tests designed to obtain information on the stability of the pharmaceutical product in order to define its shelf life and utilization period under specified packaging and storage conditions. conditions namely 30 ℃ ± 0.5/ 60 ± 1 % RH and 40 ℃ ± 0.5/ 75 ± 1 % RH. The films were evaluated for weight, phenobarbital content and *in vitro* drug release after storage for 10, 20 and 30 d. [16]

Results and Discussion

Optimized formulations F1- F7 were subjected to various evaluation parameters. The thicknesses, percentage weight variation, tensile strength and hydration ratios of formulated films are tabulated in Table 2. The values are almost uniform in all formulations. Obtained results has shown that increase in film thickness decreases tensile strength while increases % elongation. Further increases in thickness of film increases crystallinity of film and decrease dissolution rate. All the films passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5%. The hydration ratio defines the ability of films to absorb water from environment or from dissolution media. Increase in concentration of superdisintegrants increases hydration ratio or water uptake and decrease disintegration and dissolution time. F3 and F6 formulations showed higher hydration ratio while F1 formulation shows low hydration ratio.

Tensile strength and content uniformity of all prepared formulation is shown in Table 3. Results revealed that formulations showed better tensile strength and less to moderate % elongation. Tensile strength was found in range of 0.462 ± 0.007 kg/mm^2 to 0.808 ± 0.004 kg/mm^2. There is no significant change in the tensile strength of all formulations. An

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optimum concentration of superdisintegrants showed improvement of tensile strength, but at higher concentration there was no further increase in tensile strength. Higher concentration of superdisintegrants increases thickness and crystallinity of films which causes decrease in tensile strength as well as percent elongation. The results indicated that in all the formulations the drug content was uniform.

Disintegration time and dissolution time of formulated films is tabulated in Table 3. Results revealed that addition of superdisintegrants decreases the disintegration time and dissolution time. But at higher level (2%) there was no much reduction of disintegration time and dissolution time.

Cumulative drug release was calculated on the basis of drug content of phenobarbital present in the respective film. The results obtained in the *in vitro* drug release for the formulations F1 to F7 and marketed tablet "LUMINAL" are shown Figure. 1. The graph of % cumulative drug release vs. time for formulation F1, F2, F3, shows drug release up to 87.836%, 88.228%, 96.574%, respectively, at end of 14 min. Rapid drug dissolution was observed in F4, F5, F6, and F7 which release 96.307%, 86.222%, 94.44% and 95.114% respectively at end of 14 min. F3 formulation shows highest % of drug release 96.574% than other formulations. The observed rapid dissolution might be due to fast disintegration of films and rapid dissolution of drug. Increase in the concentration of superdisintegrants increases dissolution rate of drug which was observed in F3, F4, F6 formulation, but further increase in concentration of superdisintegrants will not increases dissolution rate much more which was observed in film F4, F7. Also increase in the concentration of superdisintegrants causes precipitation of films and decreases tensile strength and folding endurance. This is observed at concentration of ≥ 2% of the film. *In vitro* release rate study of F3 formulation vs. conventional marketed tablet LUMINAL containing 15 mg phenobarbital has shown that F3 release found to be faster and complete within 15 min. *In vitro* release of LUMINAL was found to be 15% in 14 min and up to 46% at half an h.

SEM was performed on the films to assess changes in their surface morphology prior to and after dissolution testing. SEM image of formulation F3 is depicted in Figure. 2a at time 0 min and Figure. 2b at time 1 min. A smooth and compact surface with crystals of phenobarbital was noted at time 0 min for the optimized film F3. As dissolution time progressed to the first minute, film appeared porous. After 1 min the surface morphology of films showed significant changes in texture, to the extent that the film developed clearly visible pores with solubilization of phenobarbital crystals.

The X-Ray diffraction study is conducted for evaluation of change in crystalline nature of pure drug by process or addition of other polymers. The X-Ray diffraction patterns of pure phenobarbital, physical mixtures, and phenobarbital film F3 are illustrated in Figure. 3a, 3b and 3c. The characteristic peaks of phenobarbital appeared at a diffraction angle of 2θ at 3.8, 7.5, 11.30 and several sharp diffraction peaks between 13.5 0 – 36.00 suggesting that the drug is present in crystalline form. The physical mixture showed the weak diffraction peaks of phenobarbital at 3.8, 7.5, 11.30 and very weak peaks from 13.50 to 26.00, indicates that the presence of various polymers may have an interaction with phenobarbital. In formulations the characteristic peaks of phenobarbital are not visible in diffractogram of F3

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film; this indicates that phenobarbital was amorphized in F3. These results revealed that change in crystallinity nature of drug may be responsible for improved dissolution rate.

F3 formulation was selected for stability studies on the basis of high cumulative % drug release and also results of *in vitro* disintegration time. The results obtained are tabulated in Table 4 and Figure. 4. From these results it was concluded that, formulations F3 is stable and retained their original properties with minor differences. The *in vitro* release profile of F3 at 30 ℃/ 60% RH and 40 ℃/ 75% RH conditions after 30 d was 95.114% and 92.316% respectively, has indicated that no or minor alteration after storage.

Conclusion

In the present study successful optimization was done to study the influence of film formers, film modifier, plasticizers and superdisintegrants (SDs) in mouth dissolving films. Mouth dissolving films of Phenobarbital could be formulated with available low viscosity film formers viz. HPMC E15, Pectin, HPC, Xanthan gum. Phenobarbital, a poorly water soluble drug could be successfully incorporated in mouth dissolving film with the help of propylene glycol as solubilizer and plasticizer. Films with low viscosity grade film formers and modifier with optimized concentration are more preferred as drug vehicle for mouth dissolving films. Use of plasticizers in combination could give better results to films in respect to physicochemical parameter like, tensile strength, % elongation, folding endurance and flexibility. Incorporation of superdisintegrants in the mouth dissolving film could be useful for rapid disintegration and dissolution time. The *in vitro* drug release, *in vitro* stability evaluation and physicochemical/ mechanical results obtained in this work, confirm the potentials of the mouth dissolving film of phenobarbital as a promising candidate for quick relief from epileptic seizures and attacks with better patient compliance, with all class of patients.

References

[1] Sharma R, Parikh KA., Gohel MC., Soniwala MM., Development of taste masked film of Valdecoxib for oral use. *Indian J Pharm Sci*. 2007; 69: 320-323.

[2] Borsadia SB, O'halloran D, Osborne JL, Quick dissolving films–A novel approach to drug delivery. *Drug Delivery Technology*. 2003; 3: 63–66.

[3] Liang AC, Chen Li-lan H, Fast-dissolving intraoral drug delivery systems. *Expert Opin Ther Pat*. 2001; 11: 981-986.

[4] Dinge A, Nagarsenker M, Formulation and evaluation of fast dissolving films for delivery of triclosan to the oral cavity, *AAPS Pharm Sci Tech* 2008; 9: 349-356.

[5] Saigal N, Baboota S, Ahuja A, Ali J, Fast-dissolving intra-oral drug delivery systems. *Expert Opin Ther Pat*. 2008; 18: 769-781.

[6] Birader SS, Bhagavati ST, Kuppasad IJ, Fast dissolving drug delivery systems: a brief overview, *Internet J pharmacol*. 2006; 4(2).

[7] Shimodaa H *et al.* Preparation of a fast dissolving oral thin film containing dexamethasone: A possible application to antiemesis during cancer chemotherapy. *Eur J Pharm Biopharm*. 2009; 73: 361-365.

[8] James O. McNamara. Drugs effective in the therapy of the epilepsies, In: Hardman JG, Limbrid LE, Goodman Gilman, et al, editors. Goodman and Gilman's 'The Pharmacological Basis of Therapeutics', 10th ed, USA: McGraw Hill Health Professions Division. 2001, pp. 521-531.

[9] Daniel HL. Seizures and Epilepsy, In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, et al, editors, Harrison's principle of internal medicine, 16th ed, USA: The McGraw-Hill Companies. 2005(2) pp. 2357.

[10] Fritz ED. The classification of epileptic seizures and the epilepsies, In: Meinardi H. editor, Handbook of clinical neurology, The epilepsies, Part I; vol 72-28, New York: Elsevier science. 1999 pp. 1- 13.

[11] Meldrum BS. Pathophysiology. In: Laidlaw J. editor, Text Book of Epilepsy, 3rd edition, London: Churchill Livingstone, Bath Press, Avon. 1988 pp. 203-227.

[12] Treiman DM, Walker MC. Treatment of seizure emergencies: Convulsive and nonconvulsive status epilepticus. *Epilepsy Research*. 2006; S77–S82.

[13] Perichard JW, Mattson RH. Barbturates: an update. In: Pedley TA, Meldrum BS. Editor. Recent advances in epilepsy, 1st ed. London: Churchill Livingstone, vol 3; 1986, pp. 261-277.

[14] Kathleen P. Martindale. The complete drug reference. 32nd ed, Pharmaceutical Press Massachusetts. 1999, pp. 351-358.

[15] Cilurzo F, Cupone IE, Minghetti P, Selmin F, Montanari L. Fast dissolving films made of maltodextrins. *Eur J Pharm Biopharm* 2008; 70: 895–900.

[16] Swamy NGN, Dharmarajan TS, Paranjothi KLK. Study of film forming properties of hydroxy propyl guar & its use in preparation of medicated transdermal patches. *Indian J Pharm Educ Res* 2008; 42: 147- 153.

[17] Jin-Wook Yoo, Dharmala K, Chi H. Lee. The physicochemical properties of mucoadhesive polymeric films developed as female controlled drug delivery system. *Int J Pharm.* 2006; 309(1-2):139-145.

[18] Tanwar YS, Chauhan CS, Sharma A, Development and evaluation of carvedilol transdermal patches. *Acta Pharm.* 2007; 57: 151-159.

[19] Perumal VA, Lutchman D, Mackraj I, Govender T. Formulation of monolayered films with drug and polymers of opposing solubilities, *Int J Pharm* 2008; 358: 184- 191.

[20] Agarwal GP, Seth AK, Saini TR. Evaluation of free films. *Indian drugs*. 1985; 23: 45-47.

[21] European Pharmacopoeia 4, 4th ed. Published by Directorate for the Quality of Medicines of the Council of Europe, Council of Europe, Strasbourg Cedex, France, 2002, pp. 197- 98.

[22] Kaewnopparat N, Jangwang A, Mancenaun D, Kooskulkunakorn L, Pongsaurupong S, Physical characterization and aging studies of fast release phenobarbital-urea solid dispersions. *Thai J Pharm Sci* 2001; 25: 121-132.

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Tables

Table 1. Compositions of phenobarbital mouth dissolving films

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7
Phenobarbital	117	117	117	117	117	117	117
METHOCEL- E 15	150	150	150	150	150	150	150
Pectin	50	50	50	50	50	50	50
HPC (low viscosity grade)	25	25	25	25	25	25	25
Menthol	40	40	40	40	40	40	40
Aspartame	3	3	3	3	3	3	3
Glycerol	125	125	125	125	125	125	125
Xanthan gum	10	10	10	10	10	10	10
Sodium starch glycolate	-	50	100	150	-	-	-
Croscarmellose sodium	-	-	-	-	50	100	150
Propylene glycol	100	100	100	100	100	100	100
Water (Q.s)	5	5	5	5	5	5	5
Ethanol (Q.s)	7	7	7	7	7	7	7

Table 2: Evaluation of mouth dissolving films of Phenobarbital

Formulation	Thickness		Mean weight	% Hydration
	Mil	Micron	mg***	ratio***
F1	2.83	13.9166 ± 0.045	110.2 ± 0.20	0.808± 0.004
F2	2.94	14.3054 ± 0.098	117.3 ± 0.25	0.727± 0.003
F3	3.19	14.2269 ± 0.023	121.8 ± 0.95	0.616± 0.002
F4	3.37	13.7665 ± 0.539	119.3 ± 0.30	0.518 ± 0.005
F5	2.98	13.9722 ± 0.050	127.2 ± 0.30	0.701± 0.001
F6	3.53	14.3334 ± 0.050	123.6 ± 0.20	0.505 ± 0.001

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F7	3.73	14.1388 ± 0.032	119.1 ± 0.20	0.462 ± 0.007

***= significance value P > 0.0001
n = average of triplicate was determined.

Table 3: Evaluation of mouth dissolving films of phenobarbital

Formulation	**Tensile strength Kg/mm^2*** **	**Drug content mg****	**Disintegration time s*** **	**Dissolution time s*** **
F1	0.808 ± 0.004	13.65 ± 0.05	31.33 ± 0.577	126.0 ± 1.0
F2	0.727 ± 0.003	16.29 ± 0.076	27.00 ± 1.00	94.00 ± 1.0
F3	0.616 ± 0.002	18.71 ± 0.26	23.33 ± 1.00	73.67 ± 1.528
F4	0.518 ± 0.005	17.13 ± 0.13	23.33 ± 1.155	72.33 ± 1.528
F5	0.701 ± 0.001	14.50 ± 0.076	28.00 ± 1.00	99.33 ± 1.528
F6	0.505 ± 0.001	19.75 ± 0.17	26.00 ± 0.577	79.33 ± 1.528
F7	0.462 ± 0.007	13.92 ± 0.047	26.00 ± 0.577	76.00 ± 2.0

*****=** significance value P > 0.0001
**= Significance value P> 0.001
n = average of triplicate was determined.

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Table 4: Stability studies – drug content, weight variation, disintegration time, dissolution time after 30 d storage of optimized formulation F3 at 30 °C/ 60% RH and 40 °C/ 75% RH

Storage condition	Tested after time (in days)	Weight variation (mg/ 3cm^2)	Disintegration time (s)	Dissolution time (s)	Drug content uniformity (n=3)
30 °C/ 60% RH	10	121.7 ±0.1	23.47 ± 0.33	72.56 ± 0.54	14.166 ± 0.029
	20	121.6±0.06	23.32 ± 0.57	73.62 ± 0.33	14.169 ± 0.029
	30	121.6±0.05	24.12 ± 0.66	73.80 ± 0.33	14.163 ± 0.311
40 °C/ 75% RH	10	121.7±0.06	22.45 ± 0.57	73.67 ± 0.33	14.139 ± 0.057
	20	121.6±0.05	23.22 ± 0.89	74.22 ± 0.66	14.139 ± 0.014
	30	121.6±0.03	23.05 ± 0.33	74.35 ± 0.64	14.139 ± 0.026

n = average of triplicate was determined.