ejpmr, 2024, 11(4), 442-446

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

FAST DISSOLVING TABLETS OF PHENYTOIN BY HOLE TECHNOLOGY

Nireeksha Shetty*, Krishnananda Kamath K., Mukesh Vishwakarma and A. R. Shabaraya

Department of Pharmaceutics, Srinivas College of Pharmacy, Valachil, Farangipete Post, Mangalore, Karnataka, India – 574143.

***Corresponding Author: Nireeksha Shetty**

Department of Pharmaceutics, Srinivas College of Pharmacy, Valachil, Farangipete Post, Mangalore, Karnataka, India – 574143.

Article Received on 29/02/2024 **Article Revised on 20/03/2024** **Article Accepted on 09/04/2024**

ABSTRACT

Research has been done to prepare Phenytoin fast dissolving tablets (FDT) by Hole technology. Once these fast-dissolving tablets contact with gastro enteric fluids, the fluid can enter the hole within the tablet and immediate disintegration of tablets takes place. Fast dissolving tablets of Phenytoin was designed with a view to provide a quick onset of action. Here fast dissolving tablets were prepared by direct compression by using super disintegrants such as Sodium Starch Glycolate and Croscarmellose Sodium. This quick disintegration of tablets is additionally influenced by the formation of space between granules. FDTs were subjected to numerous pre and post formulation parameters. From all the formulations F1, F2, F3 and F4, F3 was found to be best formulation. Evaluation parameters like hardness and friability indicates that the tablets were mechanically stable in all formulations. Its disintegration and dissolution rates were compared. At the end of 30 min formulation F3 released 98.38 % of drug and considered as best formulation. Phenytoin fast dissolving tablets prepared by hole technology using camphor as a sublimating agent and shows excellent drug release from the tablet.

KEYWORDS: Fast Dissolving Tablets, Phenytoin, Sublimation, Hole Technology.

INTRODUCTION

The conventional dosage form like tablet and capsule have wide acceptance up to 50-60% of total dosage forms. Tablet is still most popular conventional dosage forms existing today because of ease of self-administration. easy to manufacture and it can be delivered in accurate dose. Fast dissolving drug delivery systems (FDDS) are a new generation of formulations which combine the advantages of both liquid and conventional tablet formulations and at the same time, offer added advantages over both the traditional dosage forms.[1] The target population of these fast-dissolving forms have generally been paediatric, geriatric, and bedridden or disabled patients. Patients with persistent nausea, who are travelling or who have no access to water are also good candidates for FDTs.[2] These tablets usually dissolve within 15-30 min. The faster the drug goes into solution, quicker the absorption and onset of clinical effect.[3]

Epilepsy is one of the most common neurological diseases, with about 50 million patients globally. Phenytoin is one of the potential candidates for epilepsy treatment, but it has low bioavailability due to lower aqueous solubility. Fosphenytoin, a prodrug is widely used to overcome the low bioavailability problem of phenytoin. High cost, transient paraesthesia and pruritus are some of the disadvantages of fosphenytoin over phenytoin.[4] Phenytoin used for the acute management of severe seizures and have a rapid onset of action once delivered into the central nervous system and are safe. Phenytoin, is included in the "WHO Essential Drug list" for the treatment of convulsion and epileptic seizure. Although intravenous therapy is the most rapid way to suppress epileptic convulsion, it may produce toxic manifestation due to excessive drug concentration, requires great care and caution to avoid thrombophlebitis and irritation and may not be feasible where adequate medical facilities are not available in the immediate vicinity. While absorption of phenytoin from intramuscular route is poor and erratic, the time to reach peak plasma concentration following oral administration is 1-2 hours and is accompanied with acid hydrolysis and extensive liver metabolism. If Phenytoin is formulated in a fast-dissolving tablet dosage form, the high vascularity and rich blood supply of oral mucosa may provide rapid absorption and faster onset of action and could enable a patient for self-medication even without the aid of water in a situation where onset of convulsion is apprehended. Valuable research reports for formulation of rapidly disintegrating tablets are available; also, various technologies for improving dissolution property of poorly water-soluble drugs have been documented to enhance bioavailability following oral absorption.[5]

Hole technology

The main objective of this technology is to design and develop Fast dissolving tablets by novel hole technology. It is a novel approach to decrease the disintegration time and increase the patient compliance. By using this technology absolute surface area of the tablet increase due to hole formation. Immediate breaking of the tablet takes place as the fluid enters the hole formed in the tablet. Several technologies were developed to enhance the disintegration time but the tablets prepared by hole technology have increased surface area due to formation of hole and increased pore structure Fig 01. The main principle involved in hole technology is sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane, and phthalic anhydride may be compressed along with other excipients into a tablet. This volatile material is then removed by sublimation leaving behind a highly porous matrix.[6]

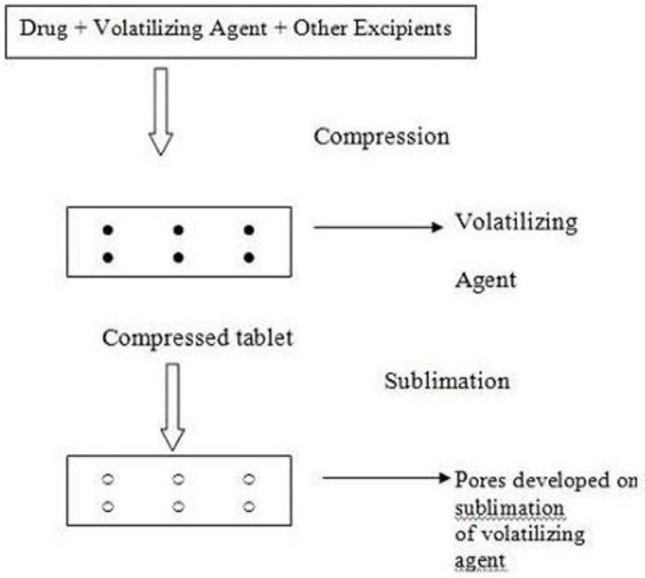

Fig. 01: Development of Fast dissolving tablets by novel hole technology.

MATERIALS AND METHODS

Materials

Phenytoin was purchased from Yarrow Chem Products, Sodium starch glycolate, Mannitol, Magnesium stearate was purchased from Himedia laboratories. Croscarmellose sodium was purchased from Yarrow Chem Products and Lactose was purchased from Medilise Chemicals.

Methods

Preparation of FDTs by Hole technology

Phenytoin sodium, Sodium starch glycolate, Croscarmellose sodium, Lactose and Mannitol were mixed in a container. Talc and Magnesium stearate after passing through sieve #60 is mixed and blended with initial mixer in the container. Camphor is then mixed with this powder blend. This blended granules compressed into tablets. After compression these tablets were dried at 60ºC by keeping the tablets in a hot air oven until complete removal of camphor.[6-8]

Table No. 1: Formulation chart for tablets.

Ingredients (mg)	F1	F2	F3	F4
Phenytoin	50	50	50	50
Croscarmellose sodium	8	16	-	-
Sodium starch glycolate	-	-	8	16
Lactose	46	46	46	46
Mannitol	92	84	92	84
Talc	2	2	2	2
Magnesium stearate	2	2	2	2
Camphor	50	50	50	50
Total	250	250	250	250

Evaluation of Fast Dissolving Tablets[9-17]

Tablets were evaluated for Weight variation, Hardness, Thickness and friability using standard procedures.

Disintegration test

The disintegration time was determined using disintegration test apparatus. One tablet was placed in

each of the six tubes of the apparatus and disc was added to each tube. The bath temperature-maintained 37±2°C. The time taken for the complete disintegration of the tablet with no palpable mass remaining in the basket was measured and recorded.

Dissolution test

USP Type II Paddle apparatus was used and paddle was allowed to rotate at 50 rpm. pH 6.8 Phosphate buffer was used as a dissolution medium. Determination of amount of drug dissolved from tablets was carried by UV spectrophotometer at 242nm.

***In-vitro* drug release studies details**

Apparatus used : USP Type II dissolution test apparatus
Dissolution medium : 6.8 pH Phosphate buffer
Dissolution medium volume : 500 ml
Temperature : 37±0.5° C
Speed of basket paddle : 50 rpm
Sample withdrawn : 5 ml
Absorbance measured : 242 nm

RESULTS AND DISCUSSION

Organoleptic properties of drug

It was found that Phenytoin is a fine white crystalline powder, odourless and was found to be within the reported literature limits. The results obtained were shown in table 2.

Table No 2: Organoleptic properties of Phenytoin.

Properties	Result
Description	Fine white, Crystalline
Odour	Odorless
Colour	White
Melting Point	296.5℃
Solubility	Water-insoluble Ethanol-Soluble

Standard plot of Phenytoin in PBS pH 6.8.

The values of the absorbance at different concentration (µg/ml) in phosphate buffer pH 6.8 are given in Table 3 and the standard plot is shown in Fig.2. The absorbance value remained linear and obeyed Beer's Lamberts Law in the range of 0-30 µg/ml with the R^2 value of 0.9961.

Table No 3: Calibration data of Phenytoin at 242 nm in PBS pH 6.8.

Concentration (µg/ml)	Absorbance
5	0.054±0.002
10	0.132±0.006
15	0.206±0.017
20	0.265±0.012
25	0.325±0.020
30	0.402±0.013

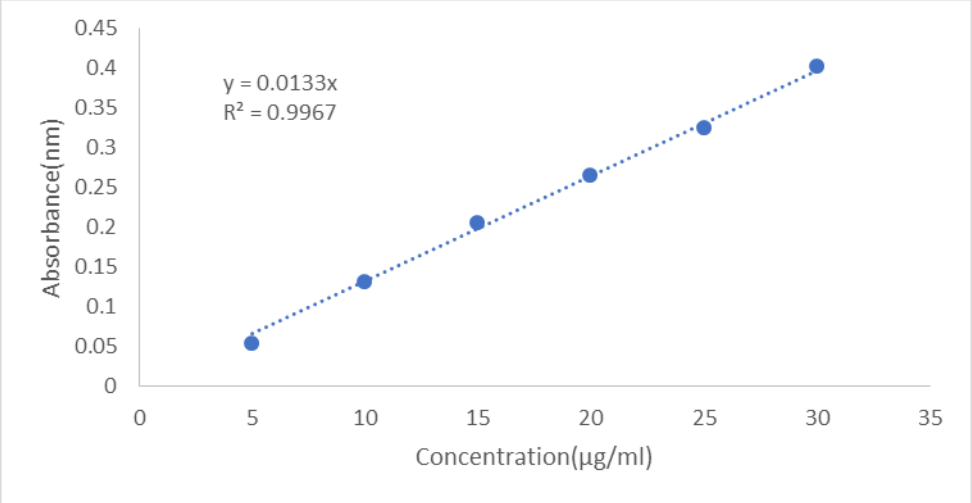

Fig 2: Calibration Curve of Phenytoin.

Determination of Size, Bulk density, Compressibility index, Angle of repose, Rate of flow: Physical properties of prepared tablet granules evaluated for Size, Densities, Compressibility Index, and flow properties like Angle of repose and Rate of Flow showed within the standard limits.

Table No 4: Angle of repose, Bulk density, Tapped density, %Compressibility & Hausner ratio.

Formulation	$\vartheta=\tan^{-1}$ (h/r)	Bulk Density(g/ml)	Tapped Density(g/ml)	%Compressibility	Hausner Ratio
F1	35°3'	0.47	0.62	28.84%	1.31
F2	43°7'	0.45	0.61	26.00%	1.35
F3	30°9'	0.46	0.68	31.70%	1.46
F4	33°8'	0.41	0.60	31.80%	1.46

Post Formulation Studies

a. Weight variation

The average weight of twenty tablets was calculated for each formulation which was ranged from 241.5 mg to 245.9 mg. The weight variations of all the formulations were depicted in Table no.5.

b. Thickness

The thickness for all the formulations F1 to F4 was ranged from 4.26 to 4.31 mm which showed that there is no significant difference in thickness of all formulations. Thickness of all formulations were depicted in Table no.5.

c. Hardness

The hardness for all the formulations F1 to F4 was ranged from 3 to 3.5 kg/cm^2 which showed that there was no significant difference in hardness of formulations.

d. Friability

The percentage friability of all the formulations were found to be not more than 1% which was found to be well within 1% w/w limit. Friability of all the formulations were depicted in Table no.5.

Table No 5: Weight variation, Hardness, Thickness and Friability.

Formulation	Weight variation(mg)	Hardness (KP)s	Thickness (nm)	Friability (%w/w)
F1	241.5±1.12	3.5±0.63	4.29±0.15	0.89
F2	245.2±2.05	3.3±0.54	4.26±0.14	0.54
F3	244.2±1.16	3.0±0.39	4.31±0.16	0.81
F4	245.9±1.83	3.2±1.26	4.31±0.10	1.08

e. Disintegration Test

All the formulations showed disintegration within 67 to 122 sec. As shown in the Table No.6 and fig 5. Formulation F3 showed best disintegration time 67 sec.

Table No 6: Disintegration Test.

Formulation Code	Disintegration Time(sec)
F1	122 Sec
F2	98 Sec
F3	67 Sec
F4	81 sec

***f. In vitro* drug release study**

From the dissolution studies, it was observed that the release rate of drug from tablets varied. Table No. 7 and Fig 3 shows cumulative percentage drug release from formulation F1, F2, F3 and F4 containing different concentration of super disintegrants at the end of 30 min was found to be 59.16%, 92.54%, 98.38%, 95.43% respectively. *In-vitro* release studies showed that F3 shows better release compared to other formulations.

Table No 7: *In vitro* drug release data.

Time (min)	%Drug Release			
	F1	F2	F3	F4
5	13.96±1.05	11.98±1.70	12.04±1.42	9.17±1.89
10	23.00±2.32	20.40±1.19	19.81±1.91	23.08±2.08
15	32.04±2.49	32.80±2.07	36.08±1.85	35.75±2.12
20	41.08±1.09	49.00±2.44	55.00±2.89	53.18±1.52
25	50.12±2.84	69.42±3.61	75.43±3.06	73.75±2.40
30	79.16±4.61	92.54±3.78	98.38±3.11	95.43±2.88

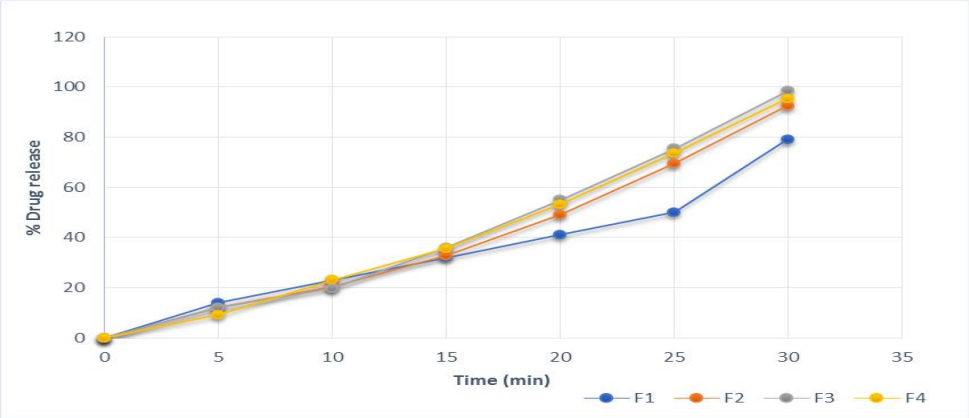

Fig 3: *In vitro* drug release study.

DISCUSSION

From the reproducible results of executed experiments, it can be concluded that; Preformulation studies of Phenytoin comply the reported literature limits. The main objective of the present research work was to improve the solubility and dissolution properties of poorly soluble drug Phenytoin. Various techniques have been used to improve the solubility and dissolution rate of poorly soluble drugs, amongst these one, Hole Technology of drug using camphor and use of super disintegrants improved solubility and dissolution rate. Evaluation parameters like hardness and friability indicates that the tablets were mechanically stable in all formulations. Percentage weight variation, disintegration time were found to be within the pharmacopoeia limits in all the formulations. At the end of 30 min formulation F3 released 98.38% of drug and considered as best formulation. F3 was selected as best formulation in comparison to other formulations. Hole Technology improves the disintegration and dissolution property.

CONCLUSION

Phenytoin fast dissolving tablets prepared by hole technology using camphor as a sublimating agent shows excellent drug release from the tablet so it shows that this method increases the porosity of the tablet and it is the one of the best methods used for the preparation of fast dissolving tablets.

ACKNOWLEDGEMENTS

Thanks to Principal and Director, Srinivas College of Pharmacy, and Shamarao Foundation Mangalore for providing facilities.

CONFLICT OF INTEREST: None.

REFERENCES

1. Shah R, Shah D, Patel CA, Keraliya RA. A comprehensive review on fast disintegrating tablets and its manufacturing techniques. International Journal Medical and Pharmaceutical Research, 2013; 2: 65-71.
2. Nandy BC, Mazumder B, Pathak K, Saxena N, Jain S, Sharma S, Amishaben R, Shrivastava A, Saxena P. An overview on fast dissolving drug delivery system. Asian Journal of pharmaceutical sciences and research, 2011; 1(2): 1-30.
3. Reddy LH, Ghosh B. Fast dissolving drug delivery systems: A review of the literature. Indian journal of pharmaceutical sciences, 2002; 64(4): 331-335.
4. Agrawal S, Gaikwad S, Patel R, Shinde L, Deshmukh A. Synthesis and Formulation Development of Phenytoin by Inclusion Complexation. Indian Journal of Pharmaceutical Sciences, 2021; 83(5): 955-62.
5. Patel MS, Patel KN, Patel AS. Formulation and Evaluation of Phenytoin Complexes For Dissolution Enhancement. Pharma Science Monitor, 2014; 5-9.
6. Damodar R, Movva B, Vinay CV. Role of Novel Hole Technology in Fast Dissolving Tablets. J mol pharm org process Res, 2014; 2(1): 1-5.
7. Jain CP, Naruka PS. Formulation and evaluation of fast dissolving tablets of valsartan. Int J Pharm Naruke Sci, 2009 Jul; 1(1): 219-26.
8. Damodar R, Movva B. Formulation and evaluation of fast dissolving tablets of diclofenac sodium by hole technology. Molecular pharmaceutics & organic process research, 2014; 2(2): 1-6.
9. Jadhav SB, Kaudewar DR, Kaminwar GS, Jadhav AB, Kshirsagar RV, Sakarkar DM. Formulation and evaluation of dispersible tablets of diltiazem hydrochloride. International Journal of PharmTech Research, 2011; 3(3): 1314-21.
10. Dinesh Mohan S, Vanitha K, Ramesh A, Srikanth G, Akila S. Formulation and evaluation of salbutamol sulphate fast dissolving tablet. International Journal of Research in Pharmaceutical and Biomedical Sciences, 2010; 1(2): 105-8.
11. Rane DR, Gulve HN, Patil VV, Thakare VM, Patil VR. Formulation and evaluation of fast dissolving tablet of albendazole. International Current Pharmaceutical Journal, 2012; 1(10): 311-6.
12. Basu B, Bagadiya A, Makwana S, Vipul V, Batt D, Dharamsi A. Formulation and evaluation of fast dissolving tablets of cinnarizine using superdisintegrant blends and subliming material. Journal of advanced pharmaceutical technology & research, 2011; 2(4): 266.
13. Zade PS, Kawtikwar PS, Sakarkar DM. Formulation, evaluation and optimization of fast dissolving tablet containing tizanidine hydrochloride. Int J Pharm Tech Res, 2009; 1(1): 34-42.
14. Patel DM, Patel SP, Patel CN. Formulation and evaluation of fast dissolving tablet containing domperidone ternary solid dispersion. International journal of pharmaceutical investigation, 2014; 4(4): 174.
15. Ejeta F, Gabriel T, Joseph NM, Belete A. Formulation, optimization and in vitro evaluation of fast disintegrating tablets of salbutamol sulphate using a combination of superdisintegrant and subliming agent. Curr Drug Deli, 2022; 19(1): 129-41.
16. Sharma D, Singh M, Kumar D, Singh G. Formulation development and evaluation of fast disintegrating tablet of cetirizine hydrochloride: a novel drug delivery for pediatrics and geriatrics. J. of pharmaceutics, 2014; 1-8.
17. Soni A, Raju L. Formulation and evaluation of fast disintegrating tablet containing hydrochlorothizide. IJPP, 2015; 2(2): 119-33.