ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: https://ijrps.com

Nifedipine Oral Disintegration Tablet: Design, Optimization, Invivo-pharmacokinetic and Stability Studies

Arindam Chatterjee[1], Shaik Mohammad Abdulla[*2], Nagarajan G[3], Birendra Shrivastava[4]

[1]Department of Pharmaceutics, School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India
[2]Research Scholar, School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India
[3]Department of Pharmaceutical Chemistry, Dr K.V. Subba Reddy Institute of Pharmacy, Kurnool, Andhra Pradesh, India
[4]School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India

Article History:

Received on: 10 Jul 2020
Revised on: 15 Aug 2020
Accepted on: 17 Aug 2020

Keywords:

Orodispersed Tablet, Nifedipine, Wet Granulation, Bioavailability, Optimization

ABSTRACT

Nifedipine has a bioavailability of 45-56 percent and a 2-hour elimination half-life. It has a 50 percent kidney excretion rate and a 5-15 percent bile excretion rate. The intention of this research is to invent and evaluate Nifedipine loaded ODT and to prove the enhancement of bioavailability. The 2^3factorial optimization design exposed about the outcome of independent variable on dependent variable throughout the formulation of Nifedipine ODT. From the records, it was accomplished that there was a good correlation between Disintegration time, Dissolution rate and super disintegration concentration. The formulation F4 (Nifedipine ODT) has achieve the goal of ODT drug delivery with desired release characteristics, cost-effective, decreased dose, effective administration and hence improved patient compliance. The invivo pharmacokinetic studies reveals that increase in $AUC_{0-\infty}$; decrease in Tmax; increase in Cmax in Nifedipine ODT shows better bioavailability and faster duration of therapeutic action than marketed Nifilat® dosage form. Nifedipine ODT was stable at various temperature, humidity conditions and there was no drastic change in evaluation parameters. That it was concluded that Oral dispersible tablet (ODT) was a suitable dosage form to enhance the solubility at the same time the bioavailability of BCS class II drugs like Nifedipine.

*Corresponding Author

Name: Shaik Mohammad Abdulla
Phone: 8988632944
Email: abdullampharm@gmail.com

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i4.4857

Production and Hosted by

IJRPS | https://ijrps.com

INTRODUCTION

Orodispersible tablets, simple dissolving tablets, mouth dissolving tablets, fast dissolving tablets, porous tablets and quick melts are all terms used to describe ODTs. The United States Pharmacopoeia (USP) has designated these dosage forms as ODTs, based on the foregoing. The word Orodispersible tablet was invented by the European Pharmacopoeia to describe tablets that spread easily in the mouth within 3 minutes before being swallowed (Kantharao *et al.*, 2019). "A solid dose material containing a therapeutic material that disintegrates fast when put upon the tongue, normally within a matter of seconds," is according to the

US Food and Drug Administration. ODTs take anywhere from just seconds to about a minute to disintegrate (Slowson and Slowson, 1985).

The ideal properties of Orodispersible tablets are compatible through taste masking and other excipients, High drug loading, It dissolves or disintegrates in the mouth in a seconds and can be swallowed without water, get a good taste in your mouth, there should be little to no residual in the mouth after oral administration, remain unaffected by environmental conditions including temperature and relative humidity (Virley and Yarwood, 1990).

On choosing drug candidates for ODT dosage forms, there are a few things to keep in mind: Medications with pharmacokinetic profiles that vary substantially from the same dose given in a standard dosage type can be a good candidate for ODT. Drugs with a large fraction of penetration in the oral cavity and pre-gastric (Reddy and Ghosh, 2002) GIT sections, as well as drugs that absorb a considerable amount of toxic metabolites by first-pass liver, gastric metabolism are a good candidate for ODT. Nifedipine has a bioavailability of 45-56 percent and a 2-hour elimination half-life. It has a 50 percent kidney excretion rate and a 5-15 percent bile excretion rate (Poonuru *et al.*, 2020). Nifedipine are converted into ODT to initiate and speed up absorption from the oral cavity onwards, increasing bioavailability by controlling feacal and kidney excretion. The drug Nifedipine is used to treat hypertension. Nifedipine will help you prevent heart failure, heart attacks, and strokes there in future high blood pressure. Nifedipine is used to treat angina, a condition that causes chest pain (Reiter, 2004).

Nifedipine is a calcium channel blocker that is a dihydropyridine. Nifedipine causes dilatation of the primary coronary and systemic arteries and lowers myocardial contractility by reducing the transmembrane input of extracellular calcium ions into myocardial and vascular smooth muscle cells. Nifedipine is a calcium channel blocker of the first generation that is used to treat hypertension and angina pectoris. Treatment with Nifedipine has been linked to a high incidence of clinically noticeable acute liver injury and a low incidence of serum enzyme elevations (Offermanns and Rosenthal, 2008).

The goal of this study is to develop and test a Nifedipine-loaded ODT and to show that it improves bioavailability through in vivo pharmacokinetic investigations.

MATERIALS AND METHODS

Nifedipine was procured as a gift substance from Aurobindo Pvt ltd. PEG 4000. Crospovidone XL10, Cross Carmellose Sodium, Sodium bicarbonate, Citric acid, Aspartame, Avicel PH 101, Magnesium stearate, Mint flavor purchased from Himedia Pvt. Ltd.

Formulation of Nifedipine ODT for Selection of Variables

Weighed required quantity of API as shown in Table 1, cross carmellose sodium (CSS) sodium bicarbonate, citric acid, aspartame, avicel, half of the required quantity of disintegrants. Sieve all the ingredients through sieve no 40 to make it uniform size distribution. Blend it in mortar and pistil to get a homogenous mixture. Add required quantity of above taste masking solution to the homogenous mixture. Sieve the wet mass through sieve no 10 followed by 22. Dry it in tray dryer at 60ºC for 10 min and to the dried granules add remaining quantity of superdisintegrants, glidants, lubricants. Punch it in a 16/32 punch to get ODT (Kumar *et al.*, 2020; Suresh and Kumaravelrajan, 2013; Hiremath and Makanapur, 2017).

Optimization by 2^3 factorial design for selection of best Nifedipine ODT

The pre-optimized variables were fixed in a 2^3 factorial design, as shown in Table 1, which was created with the help of Design Expert 9 Software from Stat-ease, Inc. in the United States, and included 8 factorial runs. It was used to see how variations in the dependent variables correlated with changes in the independent variables (Patel *et al.*, 2011; Paul *et al.*, 2011). In this optimization plan, the elucidation of the result outcome was based on a 2^3 factorial design. chosen independent variables from pre-optimization parameters are given as X1 for CCS in Nifedipine ODT; X2 for Sodium bicarbonate in mg with different concentration; X3 for different (Srenivas *et al.*, 2005) Citric acid concentration for both the Optimization design at 2-different levels code as low (-1), and high (+1). By utilizing the above variables the ODT formulation was formulated and evaluated the effect on dependent variables like Y1 –Disintegration time in seconds, Y2 - % amount of drug release (dissolution rate) and Y3 – time of drug release in min (Pfister and Ghosh, 2005; Biradar *et al.*, 2006).

In-vitro Dissolution studies

The dissolution in vitro was done with a USP type II dissolution equipment (paddle method). 900 mL of 1.2pH HCL was utilized as the dissolution medium. By holding the dissolution medium at a

temperature of $37^0C\pm 2^0C$, the paddle speed was set to 50 rpm (Brown, 2003; Aurora and Pathak, 2005). The apparatus was started after the tablets were put in the dissolution medium. 5 ml aliquots were removed at intervals of 5, 10, 20, 30, 45 and 60 min, and restore with equivalent quantities of fresh dissolution medium held at the same temperature (Sugihara *et al.*, 1986; Patricia, 2006). Whatman filter paper No-41 was used to filter each 5 mL aliquot. The absorbance of 1 ml of sample in 100 ml distilled water was measured at 350 nm for Nifedipine. The concentrations of drugs in the sample were measured using a normal calibration curve (Wilson *et al.*, 1987; Klancke, 2003).

In-vivo Pharmacokinetic studies

Grouping and Treatment of Animals with Nifedipine ODT

In a parallel plan, rats were separated into three groups of six rats each. The control group is made up of only normal rats eat a daily diet and have free access to water. The second group received a proportionate dose of 30mg commercial Nifedipine tablets, while the first received Nifedipine oral disintegration (ODT) F4 tablets (the best Nifedipine ODT that showed the best dissolution and disintegration behaviour) (Bois *et al.*, 2010).

Collection of Blood Samples After Administering Nifedipine ODT

Blood samples (approximately 1 mL) were drawn from the sinus orbital to heparinized tubes at 0, 5, 15, 30, 45 and 60 minutes after the dosage form was administered. The blood trial were centrifuged at 5000rpm for 15 min to obtain the plasma measurements, then stored at 20°C for HPLC analysis. 0.2 mL plasma test sample was removed with 1 mL acetonitrile, followed by 10 minutes of centrifugation at 3000 rpm. After that, the supernatant (100 litres) was mixed with 500 litres of acetonitrile-water-acetic acid (15/85/0.1). Finally, a 20-liter aliquot be injected into the chromatographic method (Zhao *et al.*, 2011).

The HPLC investigation of Nifedipine was carried out by the mobile phase 60:40 v/v mixture of buffer and methanol. A 250 x 4.6 mm (i.d.) 5m ODS section was used for division and quantitation. Nifedipine in bulk medication, pharmaceutical dosage form, and human blood is determined using a reverse-phase high-performance liquid chromatographic technique. At ambient temperature, chromatographic separation was performed on a prepacked purospher star, C18 (5 m, 250 x 4.6 mm) column using phosphate buffer: acetonitrile (60:40 v/v) as a mobile phase and orthophosphoric acid at 242 nm.

Non-compartmental analysis was used to conduct pharmacokinetic analysis of plasma Nifedipine concentrations using pharmacokinetic software. Maximum plasma concentration (Cmax), maximum plasma concentration time (Tmax), area under plasma concentration versus time curve from zero to 60 minutes (AUC0–t), area under plasma concentration versus time curve from zero to infinity (AUC0–α), mean residence time (MRT), Tmax, and relative bioavailability (RB) were the pharmacokinetic parameters calculated. A one-way ANOVA test was used to analyze the data, and the results were presented as mean standard deviation (SD). All statistical studies were carried out using the Prism programme version 7.0. Statistical significance was described as a P value of or less 0.05 (Kostewicz *et al.*, 2014).

Stability Studies

Stability testing is a method of demonstrating how the consistency of a drug component changes over time as a result of numerous environmental elements such as temperature, humidity, and other factors. The aim is to provide recorded proof that the tablets produced meet the finished product requirements under accelerated and long-term stability conditions (Bhutani *et al.*, 2003; Anderson and Scott, 1991).

The Design Plan is as follows

Accelerated stability testing: The sample is subjected to accelerated stability testing at 55°C for two weeks and 45°C/20°C / 75% RH for six months.

Long-term testing: For a span of 12 months, the substance was checked at 25°C percent 50% RH. Form of package. The tablets were packaged in adsorbent cotton induction sealed 30 count HDPE tubes (Bott and Oliveira, 2007; Cha *et al.*, 2001).

Optimization of Nifedipine ODT

The CSS for Nifedipine ODT were selected as the suitable disintegrating agent, which selected from preoptimization screening formulation results. The 2^3 factorial optimization design and its result are shown in Tables 1 and 2; exposed about the result of independent variable on dependent variable during the preparation of Nifedipine ODT. From the data, it was concluded that there was a strong correlation between Disintegration time, Dissolution rate and super disintegration concentration.

From the data, it was established that there was a decrease in disintegration time of ODT by enhancing the superdisintegrants concentration like cross-carmellose sodium concentration ratio. On executing the superdisintegrants vs. disintegration time in

Table 1: 2^3 Factorial Design for Optimization of Nifedipine ODT

Run	Nifedipine (mg)	Effect of Independent variables on Dependent variables					
		Independent Variables			Dependent Variables		
		Factor A: (CCS) X1 (mg)	Factor B: (Sodium bicarbonate) X2 (mg)	Factor C: (Citric acid) time X3 (min)	Y1 Disintegration time (sec)	Y2 % amount of Drug release	Y3 Time of drug release
F1	20	1/5	-1/5	-1/5	18	58.5	5
F2	20	1/5	1/10	-1/5	14	52.4	5
F3	20	1/5	1/10	1/10	18	56.6	5
F4	20	1/5	-1/5	1/10	12	101.8	5
F5	20	-1/2.5	1/10	-1/5	22	68.4	5
F6	20	-1/2..5	-1/5	1/10	26	76.0	5
F7	20	-1/2.5	1/10	1/10	18	98.6	5
F8	20	-1/2.5	-1/5	-1/5	42	58.5	5

Table 2: Comparative *in-vivo* Pharmacokinetic Studies Data between Nifedipine Treatment Groups

Parameter	Nifilat (4 mg/kg) (Marketed ifedipine formulation) - oral administration	Nifedipine ODT (F4) (4 mg/kg)- oral administration
Tmax(min)	10	5
Cmax(μg/ml)	0.138	0.182
$AUC_{0-\alpha}$ (μg/ml/h)	5.434	12.684
$F\ rel = \frac{(AUC)_{drug}.(Dose)_{std}}{(AUC)_{std}.(Dose)_{drug}}$		Enhancement of Bioavailability by 2.33%

Note: increase in $AUC_{0-\infty}$; decrease in Tmax; increase in Cmax in Nifedipine ODT goes with better bioavailability and faster duration of therapeutic action than other marketed Nifilat® dosage form

Table 3: Stability Study Data of Nifedipine ODT (F4) stored at AST 40º±2ºc / RH70±5%

Parameter Detected	Evaluation Time			
	Initial	After 1 month	After 2 months	After 3 months
Appearance	White			
Texture	Smooth			
Physical Properties*	No change			
	Drug Content (%)			
Nifedipine	98.18±2.42	98.10±2.42	98.02±2.42	97.24±2.42
	% Invitro drug release at 5 min			
Nifedipine	100.5 ± 2.34	100.5 ± 2.34	99.6 ± 2.24	99.4 ± 2.42

*Weight variation, Thickness, Hardness, Disintegration Time

Table 4: Stability Study Data of Nifedipine ODT (F4) Stored at Long term condition 60% ±5% RH for 12 months

Parameter Detected	Evaluation Time			
	Initial	After 3 months	After 6 months	After 12 months
Appearance	White			
Texture	Smooth			
Physical properties*	No change			
	Drug Content (%)			
Nifedipine	98.18±2.42	98.02±2.24	97.92±2.12	97.64±2.34
	% Invitro drug release at 5 min			
Nifedipine	100.5 ± 2.34	100.2 ± 2.12	99.98 ± 2.02	99.46 ± 2.62

*Weight variation, Thickness, Hardness, Disintegration Time

min, with ANOVA the 'P' value was establish to be <0.05 i.e. P value 0.0473 for Nifedipine ODT, which specify a significant variation in Disintegration time on enhancing the concentration of Super disintegration.

Among all the 8 formulations of Nifedipine F4 Nifedipine ODT show preferred disintegration time of about 5min and 12 min at high +1 level of super disintegration time (i.e.5 mg of CCS).

Enhance in disintegrants concentration in the formulation of ODT showed a concurrent increase in the percentage amount of drug release i.e., dissolution rate, with the decrease in disintegration time of ODT, which confirmed the good and fastest release pattern of ODT in GI fluid.

By determining it in ANOVA, the 'p' value < 0.05 i.e. P value 0.0126 for Nifedipine; which established that there was a significant alteration in percentage amount of drug release by increasing the concentration of super disintegrants.

F4 Nifedipine ODT formulation showed the required percentage amount of drug release of about 101.8± 2.6% at 5min time interval in high +1 level of super disintegration concentration. Increase in super-disintegrants concentration showed a simultaneous increase in the %amount of drug release at short time.

It was concluded F4 Nifedipine ODT shows good desired results like disintegration time and dissolution rate. The polynomial equations formed from the coefficient values as of 2^3 factorial designs was produced by the changes in the independent variable oriented to dependent variable are as follow:

DT of Nifedipine ODT = 21.875-8.125X1 Equation (1)

% amount drug release of Nifedipine ODT= 71.35 + 14.85 X1 Equation (2)

Pharmacokinetic Studies of Various Nifedipine Formulations

HPLC Results for Quantification of Nifedipine in Plasma

In-vivo pharmacokinetic studies

A calibration curve was created using multiple concentrations of Nifedipine to determine the unknown plasma drug concentration, as illustrated in Table 2 and Figure 1. By graphing the peak area and nominal concentration of Nifedipine, the linearity of the calibration curve was determined. Eight different concentrations of Nifedipine were tested for linearity (0.04, 0.08, 0.12, 0.16, 0.20, 0.24, 0.28, 0.32 μg/ml).Over the concentration range tested, the peak area expression was found to be linear. The correlation analysis, r2, was determined to be 0.998. The HPLC method with interpolation methodology was successfully employed to obtain pharmacokinetic data from unknown plasma drug concentrations after single dose delivery of Nifedipine (Nifilat) and Nifedipine ODT (F4).The unknown concentration was calculated using the peak area of the injected material. Figure 1 shows the mean plasma concentration of Nifedipine as a function of time, as well as comparative research on in-vivo plasma drug concentration profiles between commercialised Nifedipine tablet (Nifilat) and Nifedipine ODT (F4). When related to the Nifedipine commercial formulation, Nifedipine ODT (F4) accelerates the release as well as the pharmacokinetic characteristics. The pharmacokinetic parameters of commercialised Nifedipine, Nifedipine ODT (F4) with Tmax of 5 and 10min; and the maximum peak plasma concentration (Cmax) of 0.138 g/ml and 0.182 g/ml, accordingly, had a significant difference in 'p' value as 0.05. Area under Curve ($AUC_{0-\alpha}$) was established to be 5.434μg/ml/h and 12.684μg/ml/h respectively. From the *in-vivo* pharmacokinetic statistics it was completed that

increase in $AUC_{0-\infty}$; reduce in Tmax; augment in Cmax in Nifedipine ODT shows better bioavailability and faster duration of therapeutic action than other marketed Nifilat® dosage form. It was confirmed that the Nifedipine ODT (F4) formulation had a bioavailability boost of roughly 2.33 percent over the commercial Nifilat tablet when relative bioavailability was calculated using the marketed formulation as a benchmark.

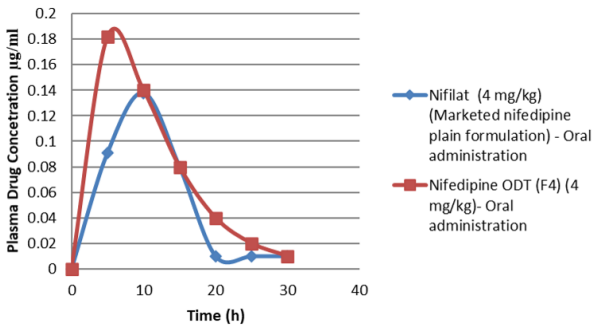

Figure 1: Graph of Comparative *in-vivo* Pharmacokinetic Study Data Between Nifedipine Treatment Groups

Stability Studies for Nifedipine ODT

The stability studies for Nifedipine ODT were performed at different conditions of temperature (Accelerated Stability testing – AST condition at 40º±2ºc and RH 70±5% and long term studies at $25^0C \pm 2^0C$ / 60% ±5%RH for 12 month) and the results were shown in Table 3 and Table 4. At three-month intervals, the parameters were assessed. The findings of stability studies revealed that the evaluation parameters of Nifedipine ODT did not alter significantly. The results showed that the Nifedipine ODT was stable at a variety of temperatures and humidity levels.

Summary

Among all Nifedipine ODT formulations, F4 possess expected release pattern and disintegration time in short time period (i.e., 101.8± 2.6% in 5^{th} min and disintegration time at 13± 2 seconds) which may fastens the absorption and bioavailability of Nifedipine. The optimized ODT not only improved the bioavailability of the drug by decreasing the drug extraction at the liver site, as evident from in-vivo pharmacokinetic studies, and may also offered substantial reduction in the systolic blood pressure in antihypertensive studies in Wistar rats. The in-vivo performance of the selected ODT was far more improved than that the available marketed product as well as the plain drug, advocating the superiority of the developed system over the marketed one.

The pharmacokinetic pharmacological evidences coupled with the results from the in-vitro parameters like disintegration time and drug release profile provide a ray of hope for a commercially viable ODT product Nifedipine to manage the hypertension related problems.

The F4 (Nifedipine ODT) formulation has achieved the objective of ODT drug delivery with desired release characteristics, cost effective, decrease dose, effective administration and hence improved patient compliance. The invivo pharmacokinetic studies reveals that increase in $AUC_{0-\infty}$; decrease in Tmax; increase in Cmax in Nifedipine ODT shows better bioavailability and faster duration of therapeutic action than other marketed Nifilat® dosage form.

From the results of stability studies, it was confirmed that Nifedipine ODT were stable at various temperature, humidity conditions and there was no drastic change in evaluation parameters of both Nifedipine ODT.

CONCLUSION

Thus, it was concluded that Oral dispersible table (ODT) was a suitable dosage form to enhance the solubility at the same time the bioavailability of BCS class II drug like Nifedipine. Nifedipine ODT (F4) achieved the goal of ODT medication delivery with desirable release characteristics, cost-effectiveness, reduced dose, and effective administration, resulting in enhanced patient compliance.

Funding Support

The authors declare that they have no funding support for this study.

Conflict of Interest

The authors declare that there is no conflict of interest for this study.

REFERENCES

Anderson, G., Scott, M. 1991. Determination of product shelf life and activation energy for five drugs of abuse. *Clinical Chemistry*, 37(3):398–402.

Aurora, J., Pathak, V. 2005. Oral disintegrating technologies: Oral disintegrating dosage forms: An overview. *Drug Deliv Technol*, 5(3):50–54.

Bhutani, H., Mariappan, T. T., Singh, S. 2003. Behavior of uptake of moisture by drugs and excipients under accelerated conditions of temperature and humidity in the absence and the presence of light-part II: Packaged and unpackaged antituberculosis drug products. *Pharmaceutical Technology*, 27(6):44–52.

Biradar, S. S., Bhagavati, S. T., Kuppasad, I. J. 2006. Fast dissolving drug delivery systems: A brief overview. *The internet journal of pharmacology*, 4(2):256–260.

Bois, F. Y., Jamei, M., Clewell, H. J. 2010. PBPK modelling of inter-individual variability in the pharmacokinetics of environmental chemicals. *Toxicology*, 278(3):256–267.

Bott, R. F., Oliveira, W. P. 2007. Storage Conditions for Stability Testing of Pharmaceuticals in Hot and Humid Regions. *Drug Development and Industrial Pharmacy*, 33(4):393–401.

Brown, D. 2003. Orally disintegrating tablets-taste over speed. *Drug Delivery Technol*, 3(6):58–61.

Cha, J., Gilmor, T., Lane, P., Ranweiler, J. S. 2001. Stability studies in Handbook of modern pharmaceutical analysis. pages 459–505. Separation Science and Technology. Elsevier .

Hiremath, S. P., Makanapur, C. 2017. Formulation and evaluation of orodispersible tablets of a model anti-hypertensive drug. *International Journal of Pharmacy and Pharmaceutical Sciences*, 9(10):34–38.

Kantharao, C. H., Swarna, K., Leelakrishna, J., Anusha, J., Asha, B., Bhavani, B. 2019. Diclofenac orodispersible tablets: formulation and In vitro evaluation. *Annal of Clinical and Laboratory Research*, 7:1–8.

Klancke, J. 2003. Dissolution Testing of Orally Disintegrating Tablets. *Dissolution Technologies*, 10(2):6–8.

Kostewicz, E. S., Aarons, L., *et al.* 2014. PBPK models for the prediction of in vivo performance of oral dosage forms. *European Journal of Pharmaceutical Sciences*, 57:300–321.

Kumar, S. A., Gowda, D. V., Sharadha, M., Akhila, A. R. 2020. The insights on Oro-dispersible tablet. *International Journal of Research in Pharmaceutical Sciences*, 11(1):260–273.

Offermanns, S., Rosenthal, W. 2008. Encyclopedia of Molecular Pharmacology. pages 596–598. 2nd edn., ISBN: 9783540389163.

Patel, N. J., Lakshmi, C. S. R., Patel, H. P., Akul, S. 2011. Formulation and evaluation of Oral dispersible tablets of cinnarizine using direct compression technique. *International Journal of Pharmaceutical Sciences and Research*, 2(4):961–967.

Patricia, V. A. 2006. Outsourcing solid-dosage manufacturing. *Pharm Tech*, 30(6):44–52.

Paul, Y., Tyagi, S., Singh, B. 2011. Formulation and evaluation of oral dispersible tablets of zidovudine with different superdisintegrants. *International Journal of Current Pharmaceutical Review and Research*, 2(2):80–85.

Pfister, W. R., Ghosh, T. K. 2005. Orally disintegrating tablets: Products, technologies, and development issues. *Pharmaceutical Technology*, 29(10):136–150.

Poonuru, R., Cheruku, R., Juluri, P., Jabeen, K., Sreeramula, S., Bandari, S., Madupu, A. 2020. Formulation and Evaluation of Orodispersible Tablets of Lamotrigineusing Discrete Super Disintegrants And Coprocessed Excipients. *International Journal of Pharmacy and Pharmaceutical Sciences*, 12(6):28–35.

Reddy, L. H., Ghosh, B. 2002. Fast dissolving drug delivery systems: A review of the literature. *Indian Journal of Pharmaceutical Sciences*, 64(4):331–336.

Reiter, M. J. 2004. Cardiovascular drug class specificity: β-blockers. *Progress in Cardiovascular Diseases*, 47(1):11–33.

Slowson, M., Slowson, S. 1985. What to do when patients cannot swallow their medications. *Pharma Times*, 51(1):90–96.

Srenivas, S. A., Dandagi, P. M., Gaded, A. P. 2005. Orodispersible tablets: Newfangled drug delivery systems-A Review. *Indian J. Pharm. Educ. Res*, 39:177–181.

Sugihara, M., Hidaka, M., Saito, A. 1986. Discriminatory features of dosage form and package. *Japanese Journal of Hospital Pharmacy*, 12(4):322–328.

Suresh, V., Kumaravelrajan, R. 2013. Formulation and Evaluation of Oral dispersible tablet of Tramadol Hydrochloride. *Int. J. Drug Dev. and Res.*, 5(3):178–186.

Virley, P., Yarwood, R. 1990. Zydis-a novel, fast dissolving dosage form. *Manufacturing Chemist*, 61:36–37.

Wilson, C. G., Washington, N., Peach, J., Murray, G. R., Kennerley, J. 1987. The behaviour of a fast-dissolving dosage form (Expidet) followed by γ-scintigraphy. *International Journal of Pharmaceutics*, 40(1-2):119–123.

Zhao, P., Zhang, L., *et al.* 2011. Applications of Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation During Regulatory Review. *Clinical Pharmacology and Therapeutics*, 89(2):259–267.