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Designing a Nitrosamines-Free Controlled Release Matrix Tablet of Paliperidone: A Quality by Design Approach

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ABS TRA C T

Paliperidone, a psychiatric medication belonging to the atypical antipsychotic family, is the 9-hydroxy metabolite of risperidone. The racemates of paliperidone are (+)- and (-)-paliperidone. It functions centrally as a dopamine D2 antagonist with serotonergic 5-HT2A antagonistic activity. Invega ER tablets are made using ALZA OROS® osmotic drug release technology. Paliperidone is administered in a specific manner over a 24-hour period using this tri-layer longitudinally compressed tablet, which is based on an advanced osmotic administration mechanism. The goal of this study is to develop a generic paliperidone controlled-release single-layer matrix tablet. In order to help create a stable and robust formulation, several combinations of Polyox and hypromellose were utilized in the core, followed by coating. The in-vitro disintegration characteristics of all strengths are comparable. Both the challenge for the alcohol dosage dumping research and the nitrosamine risk assessment were evaluated for the freeze formulation. With a pKa1 of 8.2 for the piperidine moiety and a pKa2 of 2.6 for the pyrimidine moiety, paliperidone is a basic chemical. Consequently, at healthy pH, a significant amount of the molecule is ionized. At a pH of 7.4, it is comparatively insoluble in water (0.003 g/100 mL). The solubility dramatically rises at lower pH (3 g/100 mL at pH 5.3) and falls at higher pH (0.001 g/100 mL at pH 12.9). Octanol/water's partition coefficient (log P) is 2.39. As a result, pH 2.75 buffer was determined to be the discriminating medium. The in-vitro release profile was expressed using matrix composition and the Higuchi model. In vitro release experiments show that the formulation can resist alcoholic conditions ranging from 0% to 40%. It is stable, affordable, and simple to formulate. In order to minimize the chemical interaction between an active ingredient and other excipients, the production process consists of dry mixing, compression, and coating. Therefore, the formulation has a very little chance of producing nitrosamine impurities. When it comes to dosage dumping, the formulation is categorized as tough.

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INTRODUCTION

Osmotic pump membranes should measure between 200 and 300 mm. Paliperidone, a water-insoluble antipsychotic medication that is a member of the BCS Class II drug class, is often used in the therapeutic treatment of bipolar disorder, schizophrenia, and irritability in children [1]. [2] Novel osmotic-based drug delivery system formulations for antipsychotic medications have gained popularity due to their enhanced effectiveness, less side effects, and ease of administration. The OROS-based extended-release tablet of 9-hydroxyrisperidone, a risperidone active metabolite that is marketed under the name paliperidone, Invega®, shown

superior therapeutic results [3]. The semi-permeable, however, thick to tolerate internal device pressure. [4] The water penetration rate is decreased by these thick coatings, especially for moderately and poorly soluble medications. Therefore, very water-soluble medications may be used with these thick coating devices. On the other hand, while thin coating increases permeability, there is a chance that the coating process may perform poorly, leading to film flaws. The size of the drug delivery orifice is a crucial factor that directly affects the effectiveness of the drug delivery system. There may be a chance of dosage dumping, which might lead to a higher than necessary blood concentration of the medication and possible toxicity. [5]Manufacturing of osmotic tablets is a complex as well as multi-unit operation.

Polymer-based hydrophilic matrices have attracted considerable attention in recent years as controlled-release devices for the delivery of drugs.[6] Polyethylene oxide (POLYOX®) has been commonly used in the formulation of controlled release monolithic matrix, owing to their solubility in water, availability in a range of molecular weight and viscosity grades, FDA acceptance, and unique swelling/erosion characteristics which can be utilized in modulating drug release profiles.[7] The swelling rate and erosion of POLYOX®-based matrix tablet[8] are affected by numerous other parameters such as different molecular weights, the structure of the device appears, drug solubility/loading, and the incorporation of HPMC. It's easy to manufacture, cost-effective and safe in use. Hydroxypropyl methylcellulose (HPMC, hydrophilic) has been a popular release-retarding polymer in simple matrix tablets.[9, 10] Blending of HPMC with Polyox has been recommended for the alteration of its functionalities. In this study, single layer matrix formulation of paliperidone has been prepared and evaluated against osmotic based marketed product Invega®.[11] To get the *in-vivo* bioequivalent formulation, dissolution discriminating media has been identified.[12] The effect of commonly imbibed alcohol concentrations was evaluated on drug release performance of the formulation. Alcohol concentrations of up to 40% (wt./wt.) were used, equivalent to those present in undiluted spirits such as whisky and vodka.[13]

It will be applicable in pharmaceutical industries due to major parameters such as cost-effectiveness, robustness, no dose dumping effect and easy to manufacture. These are candid parameters in pharmaceutical industries. In the past, no such study observed where single-layer matrix formulation developed have been developed against OROS.

MATERIALS AND METHODS

SUN Pharma, Vadodara, sent a complimentary sample of paliperidone. Colorcon Asia Ltd. India kindly sent gift samples of various grades of Polyox and hypromellose. For in-vitro research, 6 mg paliperidone OROS Invega® tablets served as the reference tablet. Methanol and HPLC-grade acetonitrile (Merck, Germany) were bought from the local market's authorized vendor. Analytical-grade compounds were also used.

Evaluation Parameters

Preparation of tablets

varying grades of Polyox and Hypromellose were blended in varying quantities to create two distinct prototype formulations, F1 and F2. To choose the right polymer grade in the right combination, a comprehensive screen design was used. According to early tests, the first four of the thirteen runs were completed, as shown in Table 1.

Table 1: Trial batches of prototype F1 and F2 formulation

	Trial 1	*Trial 2*	*Trial 3*	*Trial 4*
HPMC K100 LVCR	35%	17.5%	-	17.5%
Polyox WSR N80NF	-	17.5%	17.5%	-
Polyox WSR 301 NF	-	-	-	17.5%
HPMC K4M Premium	-	-	17.5%	-

The combination that would be most successful in regulating the release in modified SGF medium was determined based on core tablet dissolution data. Two prototypes have also been made. Polyox WSR N 80 NF and hypromellose K4M made up the prototype F1 blend, whereas Polyox WSR301 NF and hypromellose K100LVCR made up the prototype F2 mix. Table 2. After completely mixing the polymeric blends with a predetermined fixed quantity of lactose anhydrous and paliperidone, magnesium stearate was used to lubricate them. Since the drug content in the core tablet was around 3.0% w/w, geometrical mixing was

used to solve the content consistency issues in both prototype formulations. A conventional concave punch, 8.00 mm circular, was used to compress the powder mix. Drug release qualities are significantly impacted by formulation factors including the polyox molecular weight and the polyox to hydroxyllose ratio. [14] The concentration of hypromellose in both prototype formulations was assessed between 12.5 and 22.5%, whereas the content of Polyox, regardless of grade, was assessed between 17.5 and 32.5%. Additionally, Prototype 1's functional coat of ethyl cellulose and hypromellose in a 60:40 ratio was tuned for varying weight increase, whereas Prototype 2's formulation used methacrylic acid copolymer[15] (Acryleze) as a functional coat that was tailored for varying weight gain levels. Each tablet has a 7–8% w/w functional coating and 6 mg of paliperidone. Physical-chemical analysis of tablets and powder mixtures The compressibility and f low of the powder combination were assessed [16]. A fixed funnel was used to measure the powder mixture's angle of repose (AR), and a 100 mL cylinder was used to measure the compressibility index (CI) and Hausner's ratio (HR) in compliance with USP XXX. A Dr. Schleuniger hardness tester was used to measure the tablets' physical dimensions and hardness, while a friability tester (Electrolab, India) was used to assess the tablets' friability. Weight variation was calculated using the methodology described in USP XXX. Using a type II paddle dissolving equipment (Electrolab, India) running at 100 rpm, drug release tests were carried out in 500 mL of Modified SGF, pH 1.0 [NaCl (0.2% w/w) in 0.0825 N HCl at thermostatically regulated temperatures of 37 ± 0.5°C.

Table 2: Prototype 1and 2 final formulation compositions

S. No	*Ingredients*	*Prototype F1*	*Prototype F2*
		%w/w	*%w/w*
1	Paliperidone USP	2.86	2.86
2	Lactose anhydrous	39.04	46.19
3	Polyox WSR N80	30.95	-
4	Polyox WSR 301 NF	-	23.81
5	HPMC K100 P LVCR	-	16.67
6	HPMC (Methocel K4M)	16.67	-
7	Magnesium Stearate	0.95	0.95
	Functional Coating/Seal Coating		
8	Ethyl cellulose (Ethocel)	2.45	-
9	HPMC (Methocel E3 LV	1.63	- HPMC)
10	Tri ethyl citrate	0.61	-
11	Talc	1.02	-
12	Opadry yellow (Macrogol and Hypromellose)		
13	Acryl Eze Pink Powder 93O54222 (copolymer of methacrylic acid)	3.819.52	

where Rt and Tt represent the percentage of medicine dissolved at each time point for the reference and test tablets, respectively, Wt is an optional weight factor, and n is the number of data points gathered. Additionally, prolonged drug release was created with careful control over drug release in mind. Drinking alcohol concurrently with oral controlled-release formulations raises major safety concerns since alcohol may change the dosage form's release rate regulating mechanism, potentially leading to an uncontrolled and instantaneous drug release. Therefore, up to 40% of ethanolic medium should be used for in-vitro drug release investigations of controlled-release dosage forms, according to the Food and Drug Administration (FDA). [18] This was achieved by encasing the medication in a matrix containing an appropriate polymer that controls drug release and prevents dosage dumping. [19] Paliperidone was released from matrix tablets using the USPII paddle process, which included a dissolution apparatus. The tablets were added into 500 mL of Modified SGF, pH 1.0 [NaCl (0.2% w/w) in 0.0825N

HCl] at 37 ± 0.5°C and with a paddle speed of 50 rpm. Each sample (10 mL) was withdrawn at defined time intervals, and the same volume of dissolution medium was compensated. Samples were filtered using a 0.45 µm PVDF filter and were assayed for paliperidone by HPLC.
Weight of Coated Tablets = 210.00 210.00

Similar dissolving medium were used to replace the removed samples. Using the HPLC technique, the percentage of drug release was examined after 1, 2, 4, 6, 8, 12, 16, 20, and 24 hours. The release rate (K) and coefficient of determination (R2) were calculated by fitting the drug release data to the standard kinetic models, which include zero-order, first-order, Higuchi's square root of time, and Hixon Crowell's cube root of time. [17] The linearity of the drug release curves (coefficient of determination, R2) and release exponent (n) were ascertained using Korsemeyer–Peppas's equation, which is as follows:

The HPLC system has a UV detector. Using a C18 (150 x 4.6 mm), 5 µm, or comparable, paliperidone was examined. The mobile phase was pumped at a flow rate of 1.5 mL/min and was composed of methanol and buffer in an 85:15% v/v ratio. 275 nm was the wavelength of detection. Paliperidone is a weakly alkaline medication that dissolves at a pH-dependent pace; test formulation prototypes dissolve at the quickest rate in a pH 1.0 dissolving medium and at the slowest rate at a pH 6.8. Using Hypromellose K100 LVCR either by itself (Trial 1) or in conjunction with Polyox WSR NF 80 (Trial 2) resulted in quicker drug release. But in the presence of

Korsemeyer Pappas's equation; $Q_t/Q_\infty = kt^n$ (1)

of high viscosity Polyox WSR 301, control release of drug was observed. Comparative drug release profile of all

Here In Korsemeyer's model, k is a release constant that incorporates the system's structural and geometric properties; n is the release exponent, which indicates the drug release mechanism; Qt is the percentage of drug release at time t; Q∞ is the percentage of drug release after infinite time, typically taken as 100; and Qt/Q∞ is the fraction of drug released at time t. Utilizing the model-independent method of similarity factor f2 as a determinant parameter, the release profiles of prototype 1 and prototype 2 formulations were also examined in dissolving medium of modified SGF, pH 1.0 [NaCl (0.2% w/w) in 0.0825 N HCl].

$$f_2 = 50\log\left\{\left[1+\frac{1}{n}W_t\sum_{t=1}^{n}(R_t-T_t)^2\right]^{-0.5}\times 100\right\} \quad (2)$$

combinations are shown in Table 3 and Fig. 1. It could infer that hypromellose is the primary cause of retardation. Trials were also conducted using low-viscosity Polyox and high-viscosity hypromellose, and vice versa. When the medium pH was 1, the tablets could release the medication entirely; nevertheless, prototype 1 (which contains Polyox WSR)

Table 3: Initial screening design drug release was observed in modified SGF, pH 1.0

S. No	*Trials*	*2 hours*	*4 hours*	*8 hours*	*12 hours*
1	Trial 1	50.1	98.7	-	-
2	Trial 2	92.0	97.5	-	-
3	Trial 3	35.1	63.0	85.1	92.0
4	Trial 4	61.0	79.7	83.8	95.2

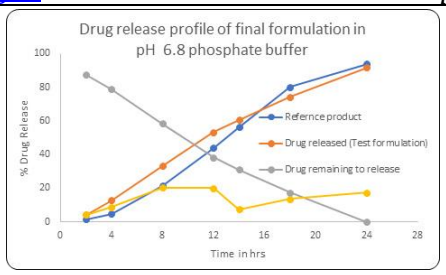

Fig. 1: Drug release of Prototype 2 (final formulation) drug release in pH 6.8 phosphate buffer

While the drug release from prototype 2 formulation (which contains Polyox WSR 301 NF and HPMC K100 P LVCR) is comparable to that of the reference formulation, the N80 and HPMC K4M formulation only released less than 70% after 24 hours when the medium pH was 6.8. Since the commercial Invega® pills are osmotic pump tablets, they don't rely on pH. Because of enteric coating, the drug's pH dependence has been adjusted in the prototype 2 test formulation. Furthermore, it has been determined that dissolution discriminatory media exist. Paliperidone's pKa value of 8.2 for the piperidine moiety and 2.6 for the pyrimidine moiety indicates that the drug has been dissolved in a pH 2.75 buffer. The buffer with a pH of 2.75 was shown to be more discriminating. Prototype 2 has a similarity factor (F2 Value) of 60 in discriminating medium, but Prototype 1 has a quicker drug release compared to the reference drug product. The optimum match for the bioequivalence investigation was assessed by conducting drug release at 4, 8, 12, and 24 hours in discriminating medium.
The tablets' ability to absorb dissolving medium and comprehend the wetting nature of polymers was assessed (Water absorption research). [20] The samples were put in 500 mL of Modified SGF, pH 1.0 [NaCl (0.2% w/w) in 0.0825N HCl] at 37 ± 0.5°C, and the paddle was agitated at 50 rpm in order to perform the tests using the dissolving equipment. The pills were taken out of the medium at different intervals, the extra liquid was drained out, and the tablets were weighed. Samples were dried at 60°C until their weight remained constant. Fresh pills were utilized at each time point, and six distinct tablets were measured at each time point. Erosion was calculated using the percentage of the removing mass (RM) as an indication. The process of water intake and expansion as the weight of the tablets rose owing to the absorbed liquid was explained by water absorption (WA).
The following formula was used to determine RM and WA:

$$RM\ (\%) = (w_o - w_r / w_o) \times 100$$
$$WA\ (\%) = (w_t - w_r / w_r) \times 100$$

where W_0 is the original weight of the dry tablet; W_r is the weight of the remaining dried tablet after entering the media at time t; W_t is the weight of tablet without water on the surface at time t before drying.

While n value (the release exponent) as response variables were calculated from experimental data for Qt/Q_∞ 0.6 using Korsmeyer-Peppas Equation to investigate the effect of factor on the drug release kinetics and mechanism:

$$Q_t/ Q_\infty \text{ ------- } kt^n = \log Q_t / Q_\infty \text{ ----- } = \log k + n \log t$$

where Q_t/Q_∞ is the fraction of the drug release at time t, k is the release constant, and n is the release exponent indicating the mechanism of drug release. Considering the cylindrical shape of the tablets, $0.89<n<1.0$ indicates the zero-order drug release kinetics, while $0.45<n<0.89$ shows anomalous release kinetics.[21]
There was no dose dumping observed in the ethanolic solution. The drug (Paliperidone) is having highest solubility in 0.1 N HCl. The addition of ethanol in water or
0.1 N HCl will reduce the solubility.[22] So, there is very least possibility of dose dumping. Further, it depends on the matrix system and product design so *in-vitro*, optimized formulation was examined in 0.1 N HCl with 40% V/V alcohol considering the worst condition. Drug release of final formulation composition in 0.1 N HCl with 40 % v/v alcohol has shown in Fig. 2.
The effect of polymer concentration and how it impacts drug release was also evaluated as part of optimization trials.

When Polyox WSR 301 is completely replaced with Hypromellose concentration, the drug is completely released in 12 hours. So, the optimum concentration of polymer combinations requires controlling the drug release and matching the release profile with the reference drug product.

Bio-waivers are used when multiple strengths are in development[23] to obtain a Biowaiver is very important with respect to industry because of the substantial savings in resources and time. The aim is to develop the BCS-based biowaiver approach as reflected by the US FDA, the EMA and the Health CANADA regarding eligibility and requirements for testing. The criteria include both proportionality of formulations as well as comparative dissolution profiles. Differences in the proportion of excipients are considered to be minor when the differences in amounts for excipients of particular functions are within the limits. The rate and extent of absorption is controlled by dissolution as a formulation factor and solubility and permeability as drug substance parameters. If the predefined criteria for these factors are met, a biowaiver can be granted. Product containing similar amount of the same excipients as the test product, sameness of the manufacturing method and quality of the test product. The drug content or potency difference between the test and comparator products should be less than 5% w/w. In conclusion, bio-waivers have opportunities when science- and risk-based approaches are used to develop products. Polyox and HPMC are hydrophilic polymers and significantly provide desire-controlled release profiles in optimum concentrations. Drug releasing rate can be further

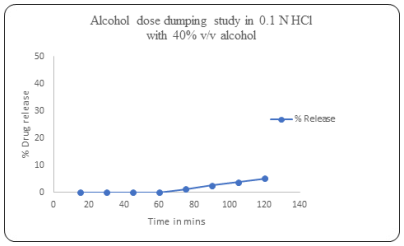

Fig. 2: Drug release of Prototype 2 (final formulation) in 0.1 N HCl with 40% v/v alcohol

suppressed as the polymer's viscosity rises. The viscosity of HPMC grade is the primary determinant of the release rate. The medication release from the Prototype 1 formulation in the pH 6.8 phosphate buffer is not full. The complete drug release seen in prototype 2 formulation (HPMCK100 P LVCR with a viscosity of 100 cp and Polyox WSR 300NF with a viscosity of 1650 to 5500 cp) is caused by the high viscosity of the polymers (HPMCK4M has a viscosity of approximately 4000 cp and Polyox WSR N80 has a viscosity of 65 to 115 cp). In this instance, it was discovered that the viscosity grade of HPMC had a major impact on the release rate. This may be explained by the fact that more water is needed to obtain a hydration condition of the core layer due to the greater viscosity grade of HPMC. Lower erosion and medication release rates were the outcome of materials' decreasing water permeability as their viscosity increased. The findings demonstrated that the use of HPMC-K100LVCR and Polyox WSR 301 NF as the materials produced the best release rate, with full dissolution at 24 hours. The requisite dissolution (of the reference medication product) in modified SGF medium was effectively accomplished using the single-layer technique to extended-release drug delivery formulation. Additionally, discriminating media have been shown to maximize the solubility of the final formulation. Acidic media with a pH of 2.75 have been chosen as dissolution discriminating media based on drug pKa. Paliperidone CR tablets were successfully made using Polyox WSR 301 NF and the hypromellose K100 P LVCR mix. The optimal concentration controlled-release test formulation tablet would be bioequivalent to INVEGA® tablets, the reference medication product. [24] It is inexpensive and simple to produce. A generic product intended for the USA and the EU must undergo bioequivalence testing against both reference items. While prolonged-release dosage forms often need three BE studies (single-dose fasting and fed and multiple dose), many drugs in the EU just need one single-dose fasted trial. As previously mentioned, two studies (single-dose fasting and fed) are often needed for immediate and modified-release dosage forms in the USA, although multiple-dose is typically not. Paliperidone's bioequivalence strength is 6 mg; thus, three and nine milligram strengths were created, and their similarity factor was assessed in comparison to the optimized formulation's 6 mg strength. The similarity factor for both the 3 and 9 mg strengths is more than 50 in

The suggested disintegration media, or modified SGF media, as
as well as buffer at pH 2.75.
The dielectric constants for ethanol and water at 20 C are 25 and 80, respectively, indicating that ethanol is less polar than pure water. The dielectric constant decreases when ethanol is added to water compared to pure water. A non-ionic

homopolymer of ethylene oxide is called polyethylene oxide (PEO). Because the ether oxygen is hydrated, PEO is soluble in water but insoluble in alcohol. [25] Drug diffusion via the enlarged hydrogel layer at the tablet surface and matrix erosion regulate drug release from the PEO matrix. [26]
The final formulation was assessed for the possibility of nitrosamines. [27] The FDA's voluntary recall of a number of medications containing Valsartan, a medication used to treat heart failure and high blood pressure, in July 2018 marked the beginning of the nitrosamine crisis. The possibly cancer-causing compound N-nitroso dimethylamine, or NDMA, was found in the marketed drug product as a result of an undocumented alteration in the manufacture of Valsartan. All marketed medications must now undergo N-nitrosamine risk evaluations, per regulatory bodies including the US FDA, Health Canada, and the European Medicines Agency. Finding possible risk sources is the first stage in a nitrosamine risk assessment. This might have to do with amine functionality that has been found in the active ingredient or ingredients, final product, or during the production process. The composition of the excipients in paliperidone extended-release tablets was examined in relation to the IPEC Europe Questionnaire (Questionnaire for excipients Nitrosamines Risk Evaluation). It does not include nitrous acid, secondary or tertiary amine sources, or solvents that contain nitrogen throughout the production process, according to a declaration obtained from the excipient producer. Therefore, it is unlikely that nitrosamine impurities will occur. [28–31]
The evaluation of inactive components and excipients used in the production process of paliperidone extended-release formulations is based only on the data and evaluation obtained from the suppliers. Nitrosamine impurities are not produced by the interaction of Paliperidone API, excipient functional groups, and manufacturing process conditions. Because of this, it is unlikely that N-Nitrosamine impurities such as NDMA, NDEA, NEIPA, NDIPA, NDBA, NMBA, and other N-Nitrosamines would occur in the final paliperidone extended-release formulation.
In summary, the reference drug product (Invega) is equivalent to the in-vitro drug release of the test formulation (matrix based). Additionally, discriminating dissolution media have been used to evaluate it. The matrix formulation method is easy to create and reasonably priced. It is essential to thoroughly examine the physicochemical critical elements, such as solubility, wettability, swellability, and mechanical properties, in order to create a strong and alcohol-resistant dosage form.

features of the final dosage form, including as its hardness, swelling, and drug release, as well as those of the API and excipients. The final formulation has also undergone nitrosamine risk evaluation. In summary, it is a single-layer matrix formulation that is comparable to the osmotic-based drug delivery system found in the reference medicine product. At first appearance, moving a generic oral human medication's dossier from the USA to the EU, or vice versa, seems to be a simple, fast, and affordable opportunity that ought to be seized. But as is always the case, things are more complicated than they seem.
Citations

References

1. Lakshmi V, Sunitha N, Babu SM. Formulation, optimization and evaluation of self nanoemulsifying drug delivery system of paliperidone. IP Int J Compr Adv Pharmacol 2022;7(3):115-122.
2. Naguy A, Adel T, Almazeedi I. Paliperidone Use in Child Psychiatry: Evidence or Diffidence? Pharmacology. 2019;104(1-2):67-70. doi: 10.1159/000500629. Epub 2019 May 16. PMID: 31096228.
3. Spina E, Cavallaro R. The pharmacology and safety of paliperidone extended-release in the treatment of schizophrenia. Expert Opin Drug Saf. 2007 Nov;6(6):651-62. doi: 10.1517/14740338.6.6.651. PMID: 17967154.
4. Patel H, Parikh VP. An overview of Osmotic drug delivery system: An update review. International Journal of Bioassays. 2017; 6.7:5426-5436
5. A lmoshari Y. Osmotic Pump Drug Deliver y Systems— A Comprehensive Review. Pharmaceuticals [Internet] 2022; 15(11): 1430. Available from: http://dx.doi.org/10.3390/ph15111430
6. Ghori MU, Conway BR. Hydrophilic matrices for oral control drug delivery. American Journal of Pharmacological Sciences. 2015; 3(5):103-109.
7. Vanza JD, Patel RB, Dave RR, Patel MR. Polyethylene oxide and its controlled release properties in hydrophilic matrix tablets for oral administration. Pharmaceutical Development and Technology. 2020 Nov 25;25(10):1169-87.
8. Maggi L, Segale L, Torre ML, Ochoa ME, Conte U. Dissolution behaviour of hydrophilic matrix tablets containing two different polyethylene oxides (PEOs) for the controlled release of a water-soluble drug. Dimensionality study. Biomaterials. 2002 Feb;23(4):1113-9. doi: 10.1016/s0142-9612(01)00223-x. PMID: 11791914.
9. Mašková E, Kubová K, Raimi-Abraham BT, Vllasaliu D, Vohlídalová E, Turánek J, Mašek J. Hypromellose - A traditional pharmaceutical excipient with modern applications in oral and oromucosal drug delivery. J Control Release. 2020 Aug 10;324:695-727. doi: 10.1016/j. jconrel.2020.05.045. Epub 2020 May 29. PMID: 32479845
10. Goldoozian S, Mohylyuk V, Dashevskiy A, Bodmeier R. Gel Strength of Hydrophilic Matrix Tablets in Terms of In-vitro Robustness. Pharm Res. 2021 Jul;38(7):1297-1306. doi: 10.1007/s11095-021-03068-y. Epub 2021 Jun 21. PMID:

34152536; PMCID: PMC8292303.
11. Chaplin S, Livingston M. Invega: prolonged- release paliperidone for schizophrenia. Prescriber. 2008; 19(4):13-16.
12. Gray VA. Power of the Dissolution Test in Distinguishing a Change in Dosage Form Critical Quality Attributes. AAPS PharmSciTech. 2018 Nov;19(8):3328-3332. doi: 10.1208/s12249-018-1197-7. Epub 2018 Oct 22. PMID: 30350251; PMCID: PMC6848239.
13. Traynor MJ, Brown MB, Pannala A, Beck P, Martin GP. Influence of alcohol on the release of tramadol from 24-h controlled-release formulations during in-vitro dissolution experiments. Drug Dev Ind Pharm. 2008 Aug;34(8):885-9. doi: 10.1080/03639040801929240. PMID: 18618305.
14. Man LX. Study of drug release behaviour from HPMC matrix tablets and EC coated matrix reservoir system. Department of pharmacy, National university of Singapore, 2005; 1-151.
15. Peppas NA, Klier J. Controlled release by using poly (methacrylic acid –g-ethylene glycol) hydrogels. Journal of controlled release. 1991; 16(1-2):203-214.
16. Kengar MD, Howal RS, Anudhakar DB, Nikam AV, Hasabe PS. Pysico- chemical properties of solid drugs: A review. Asian J. Pharm. Tech. 2019; 9 (1):53-59. doi: 10.5958/2231-5713.2019.00010.2
17. Yoshida R, Sakai K, Okano T, Sakurai Y. A new model for zero- order drug release I. Hydrophobic drug release from hydrophilic polymeric matrices. Polymer Journal. 1991; 23(9):1111-1121.
18. Jedinger N, Khinast J, Roblegg E. The design of controlled-release formulations resistant to alcohol-induced dose dumping--a review. Eur J Pharm Biopharm. 2014 Jul;87(2):217-26. doi: 10.1016/j. ejpb.2014.02.008. Epub 2014 Mar 5. PMID: 24613542
19. D'Souza S, Mayock S, Salt A. A review of in vivo and in-vitro aspects of alcohol-induced dose dumping. Aaps Open. 2017 Dec;3(1):1-20. https://doi.org/10.1186/s41120-017-0014-9
20. Romero AP, Caramella CA, Ronchi M, Ferarri F, Chulia D. Water uptake and force development in an optimized prolonged release formulation. International journal of pharmaceutics. 1991 Jul 21;73(3):239-248.
21. Elmas A, Akyuz G, Bergal A, Andac M, Andac O. Mathematical Modelling of Drug Release. Res. Eng. Struct. Mater., 2020; 6(4): 327-350.
22. Li A, Yalkowsky SH. Solubility of organic solutes in Ethanol / Water mixtures. Journal of Pharmaceutical Sciences. 1994; 83(12):1735- 1740.
23. Sarkar A. Types of biowaivers: A discussion. International Journal of Drug Regulatory Affairs. 2019;7(3):14-20.
24. Nokhodchi A, Raja S, Patel P, Asare-Addo K. The role of oral controlled release matrix tablets in drug delivery systems. Bioimpacts. 2012;2(4):175-87. doi: 10.5681/bi.2012.027. Epub 2012 Nov 4. PMID: 23678458; PMCID: PMC3648939.
25. Rowe RC, Sheskey P, Quinn M. Handbook of pharmaceutical excipients. Libros Digitales-Pharmaceutical Press; 2009.
26. Zhang F, McGinity JW. Properties of sustained-release tablets prepared by hot-melt extrusion. Pharmaceutical Development and Technology. 1999 Jan 1;4(2):241-50.
27. Schlingemann J, Burns MJ, Ponting DJ, Avila CM, Romero NE, Jaywant MA, Smith GF, Ashworth IW, Simon S, Saal C, Wilk A. The landscape of potential small and drug substance related nitrosamines in pharmaceuticals. Journal of Pharmaceutical Sciences. 2023 May 1;112(5):1287-304.
28. O'Brien MN, Jiang W, Wang Y, Loffredo DM. Challenges, and opportunities in the development of complex generic long-acting injectable drug products. Journal of Controlled Release. 2021 Aug 10; 336:144-58.
29. Park H, Otte A, Park K. Evolution of drug delivery systems: From 1950 to 2020 and beyond. Journal of Controlled Release. 2022 Feb 1;342:53-65.
30. Bhadale RS, Londhe VY. Paliperidone Palmitate-Loaded Zein- Maltodextrin Nanocomplex: Fabrication, Characterization, and In-vitro Release. Journal of Pharmaceutical Innovation. 2023 Feb 28:1-1.
31. Anand O, Pepin XJ, Kolhatkar V, Seo P. The use of physiologically based pharmacokinetic analyses in biopharmaceutics applications- regulatory and industry perspectives. Pharmaceutical Research. 2022 Aug;39(8):1681-700.