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INFLUENCE OF THE SUPERDISINTEGRANTS IN NIFEDIPINE RELEASE FROM OSMOTIC PUSH-PULL TABLETS

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Keywords:

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ABSTRACT: Push-pull osmotic pumps are controlled drug delivery systems for drugs with a broad range of solubilities; especially drugs that are poorly water-soluble. The aim of the present study was to evaluate the performance of the superdisintegrants (SD), crospovidone (CPVP), croscarmellose sodium (CS), and sodium starch glycolate (SSG), in push-pull tablets containing Nifedipine (NP) as a model drug. We performed an *in-vitro* dissolution test with phosphate buffer (0.05M) at pH 7.5 for 12 h. The amount of released NP was determined using a UV/Visible spectro-photometric method at a wavelength of 238 nm. At 12 h of release, the profile of CPVP- and CS-containing osmotic tablets was like that of the reference product Adalat OROS®, whereas the SSG-containing tablet showed differences. It is very important mention that in the first 6 h of the assay, all release profiles were different compared to the commercially available reference product. The tablets containing superdisintegrants showed faster drug delivery rates and a reduction in lag time.

INTRODUCTION: Osmotic push-pull systems have been broadly available since the 1980s and were developed specifically for the delivery of drugs with low water-solubility. These systems have been used mainly for drug delivery in the treatment of such diseases as hypertension, diabetes, and asthma. Push-pull osmotic pumps (PPOP) consist of a bi-layer core surrounded by a semi-permeable membrane with a delivery orifice drilled through the membrane coating **Fig. 1**.

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This type of system relies on a combined effect of hydration in its two compartments such that, initially, the drug layer draws sufficient water (pull) to form a saturated aqueous suspension or solution, which will be expulsed subsequently through the delivery orifice once the generated osmotic pressure and the swelling of the push layer [1, 2]. Among the main advantages of these systems is that drug release is not influenced by physiological conditions, such as stomach pH, peristaltic movements and food contents in the gastrointestinal tract. Furthermore, the systems exhibit a high grade of *in-vitro* and *in-vivo* correlation [3]. However, despite these advantages, these systems have certain limitations in terms of release rates of drugs with solubility lower than 0.05 g/mL or practically insoluble.

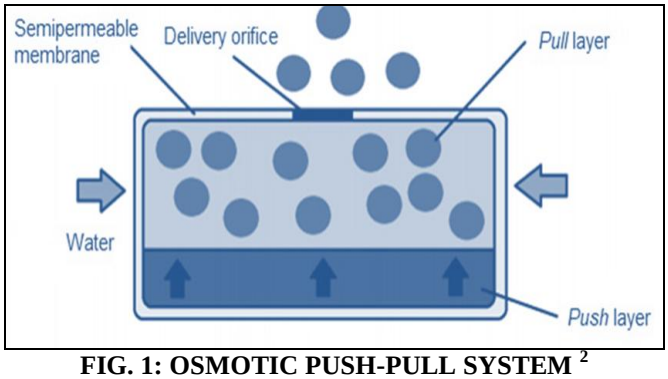

FIG. 1: OSMOTIC PUSH-PULL SYSTEM [2]

The drug-release kinetics of osmotic systems is directly related to the formation of a saturated solution or suspension within the core. Assuming a tablet core of pure drug, it would be possible to calculate the fraction of released drug according to a zero-order equation; $F(z) = 1 - S/\delta$, where S is the solubility of the drug (g/mL), and δ is the density of the tablet (g/mL). According to this equation, drugs with solubility lower than 0.05 g/mL would be released in over 95% according to zero-order kinetics. However, since drug release kinetics in osmotic systems is directly related to water solubility in the formation of a saturated solution or suspension, in the case of hydrophobic drugs, initial release rates would be very low, given the low osmotic gradient that would be generated.

Hence, it is important to consider the intrinsic solubility of a drug to design alternative formulations and include auxiliary excipients that allow modulating drug release [4]. Such alternatives might include co-compression of the drug with other excipients, coating of drug core with asymmetric membranes, use of swellable polymers, cyclodextrins nanosponges, nanoparticles or use of superdisintegrants (SD) [5, 6, 7]. Superdisintegrants allow increasing the available surface area and achieving a more rapid release of the drug substance by promoting water penetration and the breakup of the tablet into smaller fractions. They are effective at low concentrations, generally in the order of 1-10% of the total weight per unit.

Furthermore, SD improves compressibility and resistance to fracture and friability, while they have no negative impact on the mechanical force of formulations containing high doses of the drug. Water penetration and disintegration rates are factors that generally develop positively and are related to the efficiency of the SD [8].

Over 60% of new drugs currently under development are considered poorly soluble. Thus, the selection of new excipients might contribute to the increase in drug release rates and hence enhance their bioavailability. Addition of SD to push-pull osmotic systems is a viable option for optimization of drug release.

In the present work, we used Nifedipine as a model drug. Nifedipine is a poorly water-soluble antihypertensive drug that belongs to the group of calcium channel blockers of dihydropyridine derivates. Administered in an oral presentation of immediate release, Nifedipine has a short elimination half-life with significant fluctuations in plasmatic concentrations. As pertains to modified release systems, in the specific case of PPOP, Nifedipine is released 2-3 h after administration showing an initial lag time [9, 10]. The aim of the present study was to add synthetic SD to the PPOP Nifedipine core to evaluate the effects on Nifedipine release rate, as well as to observe the effects of excipients on the lag time of drug release. The superdisintegrants added were crospovidone (CPVP), croscarmellose sodium (CS), and sodium starch glycolate (SSG).

MATERIALS AND METHODS: In the present study, we used Nifedipine (Moléculas Finas de México SA de CV. Batch 0100405) as raw material and Nifedipine reference substance from the Pharmacopoeia of the United Mexican States (FEUM, Batch 60116) with 99.46% purity.

For the manufacturing of the pull layer, we used polyethylene oxide, PEO (POLYOX™ WSR N-80, Batch VL1955S511) and hydroxypropyl methylcellulose (Methocel HPMC K4M, Batch W123012 N01) as hydrophilic polymers and viscosity controllers; sodium chloride (J. T. Baker) as hydrosoluble substance and the super-disintegrants croscarmellose sodium (Solutab®, Batch 180113/ 07), sodium starch glycolate (Explosol® Batch 105019137), and crospovidone (Polyplasdone® XL, Batch 03700177318).

The push layer was manufactured using PEO (POLYOX™ WSR Coagulant, Batch XG0855S5 C3) as a swellable polymer and sodium chloride (J.T. Baker) as an osmotic agent. The components of the semipermeable membrane were 90%

cellulose acetate and 10% polyethylene glycol 4000 as plasticizer (Opadry CA®, Batch TS070852). Commercially available reference tablets, Adalat OROS® 30 mg, were acquired in the Mexican market.

Preparation of Push-Pull Tablets: In the preparation of the pull layer drug and excipients were weighed in an analytical scale (Mettler Toledo, mod. AB204-5/TAC); the components were mixed for 8 min at 9 rpm in a 500 ml twin-shell blender; 200 mg were weighed and compressed using a hydraulic press (Carver, mod. 3912) at 500 psi for 5 sec in a 9 mm matrix (see formulation in **Table 1**).

To prepare the push layer, excipients were weighed according to the formulation and mixed according to the above-mentioned conditions. We placed 100 mg of the mixture in the hydraulic press matrix, along the previously compressed pull layer to compress both layers at 500 psi for 5 sec.

TABLE 1: FORMULATIONS WITHOUT SUPER-DISINTEGRANT (NSD), FORMULATIONS THAT INCLUDED CROSPOVIDONE (CPVP), CROS-CARMELLOSE SODIUM (CS) AND SODIUM STARCH GLYCOLATE (SSG)

Formulation	NSD (% w/w)	CPVP (%w/w)	CS (% w/w)	SSG (% w/w)
Layer pull				
Nifedipine	15	15	15	15
NaCl	2	2	2	2
Polyox™ WSR N-80	76	71	71	71
Methocel HPMC K4M	7	7	7	7
Superdisintegrant	0	5	5	5
Total	100	100	100	100
Layer push				
Polyox™ WSR Coagulant	70	70	70	70
NaCl	30	30	30	30
Total	100	100	100	100

The film coating was performed in a conventional 12" pan coater at 28 °C, and the tablets were coated to 19% w/w weight gain of a semipermeable membrane. The orifice of the tablet was drilled using a mechanical drill (Pros Kit IPK-500) with 0.5 mm drill bits. Microphotographs of the orifice were taken using a scanning microscope (Jeol JSM-59000 LV) with 25 and 80X magnification.

Flowability Test of Powders Conforming the Push and Pull Layers: The following tests were carried out on the powders of the push and pull powders according to the formulation in **Table 1**.

Angle of Repose: The test was performed using the funnel method [11]. A 10 g sample of each of the push and pull mixtures were taken. The powders were left to flow freely from the top of the funnel to the bench surface.

The radius (r) and height (h) of the powder cone were used to calculate the angle of repose according to formula 1.

$$\theta = \tan^{-1} h / r \quad \text{.....1}$$

Determination of Carr's and Hausner's Indexes: These measures included the previous determination of bulk and tapped densities [11].

Bulk Density: Ten grams of the powder were taken using a measuring cylinder, and the initial volume of the powder was registered.

Tapped Density: The volume was measured after tapping the powder-containing cylinder 500 times, and the tapped volume was registered. Once the bulk and tapped densities were obtained we calculated Carr's and Hausner's indexes by applying equations 2 and 3.

$$\text{Hausner index} = \rho t / \rho b \quad \text{.....2}$$

$$\text{Carr index} = (\rho t - \rho b) / \rho t \times 100 \quad \text{.....3}$$

Where: ρt = tapped density, g/cm^3 and ρb = bulk density, g/cm^3

Evaluation of Push-Pull Tablets:

Hardness or Tablet Crushing Strength: We tested 10 tablets of each batch in a hardness tester (Pharma Alliance Group Model: PAH 01) and was reported the average and standard deviation.

Dissolution Profiles: Dissolution tests were performed using six tablets of each batch in a Hanson Research 72L dissolution tester, configured as apparatus 2 at 100 rpm with 900 ml of dissolution medium (0.05M phosphate buffer dissolution medium, pH 7.4) at 37 ± 0.5 °C. The

tablets were placed in a sinker vessel with the orifice facing the dissolution medium to ensure release; 5 ml samples were taken at 1, 2, 3, 4, 6, 8 and 12 h replenishing the medium and filtered using a 45 µm pore size filter (DISMIC-25cs). The amount of released drug was measured using a UV/Visible spectrophotometer (Cary 50) at a wavelength of 238 nm. Dissolute percentages and variation coefficients were calculated for each sampling time. Lastly, dissolution profiles were compared to the dissolution profiles obtained from batches prepared with the commercially branded Adalat OROS® using the similarity factor, *f*2 (equation 4).

$$f2 = 50log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n}(Rt-Pt)^2\right]\right\}^{-0.5} \times 100 \quad \text{.....4}$$

Where *n* is the sample number, *Rt* and *Pt* are the average dissolution percentages at the time (*t*) of the reference sample and the test sample, respectively.

Analytical Method to Assay the Dissolution Profile: Quantification of the drug was performed using a UV/visible spectrophotometer (Cary 50) at a wavelength of 238 nm. The linearity and precision of the system were evaluated in triplicate, applying a calibration curve in which 5 levels of concentration, within 60 and 140%, were determined.

Drug Release Kinetics: To determine the type of kinetics followed by the drug in our formulation we calculated the percentage of released drug against time (zero-order kinetic model, equation 5), the natural logarithm cumulative percentage of drug remaining against of time (first-order kinetic model, equation 6), and the percentage of released drug against the square root of time (Higuchi model, equation 7).

$$Q_t = k_0\, t \text{ Zero order.....5}$$

$$ln\, Q_t = lnQ_0 - k_1\, t \text{ First order.....6}$$

$$Q_t = k_H\, t^{1/2} \text{ Higuchi model.....7}$$

Where, Q_t is the amount of drug released at time *t*, Q_0 is the initial amount in the compressed tablet; k_0, k_1, and k_H are the zero-order, first-order, and Higuchi release rate constants, respectively.

The highest value of R^2 was taken as a criterion to select the appropriate model of drug release. We used the statistical package software IBM® SPSS® Statistics version 19 for statistical analysis.

RESULTS AND DISCUSSION:

Preparation of Push-Pull Tablets and Flow-ability Tests of Each Layer: Table 2 summarizes the flowability properties of the mixtures in each layer of the tablet.

TABLE 2: FLOW PROPERTIES OF THE POWDER MIXTURE CORRESPONDING TO EACH LAYER OF THE ELABORATED TABLETS

Formulation	Angle of repose (θ)	Carr´s index (%)	Hausner´s index	Type of flow*
Layer pull	28.63	9.52	1.10	Excellent
Layer push	27.38	9.98	1.11	Excellent

FEUM 2014 [11]

According to the results on the angle of repose, carr´s and Hausner's indexes, powder flowability was excellent allowing direct compression. The yield of the bi-layer tablets was 98%.

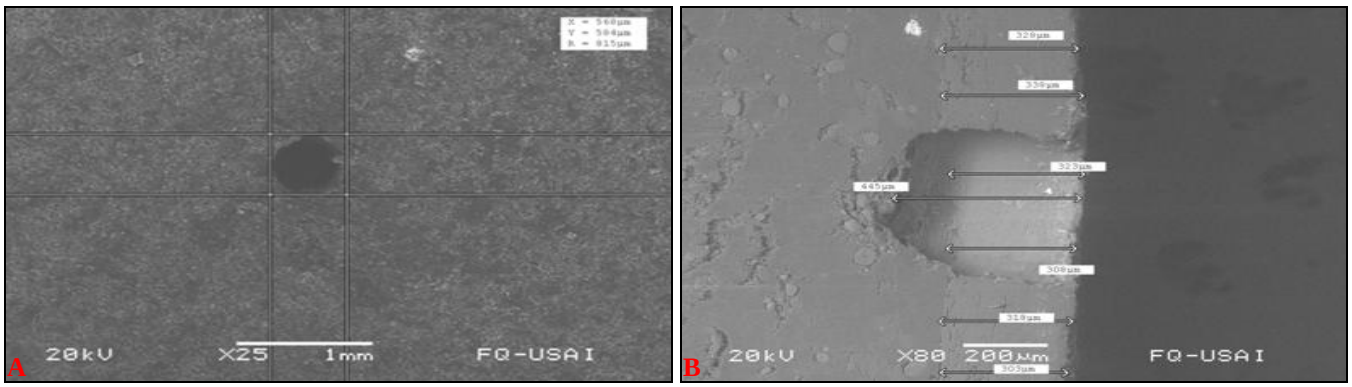

FIG. 2: MICROPHOTOGRAPHS A) CORRESPONDING TO THE SURFACE OF A PUSH-PULL TABLET ELABORATED AND B) CORRESPONDING TO THE CROSS SECTION [12]

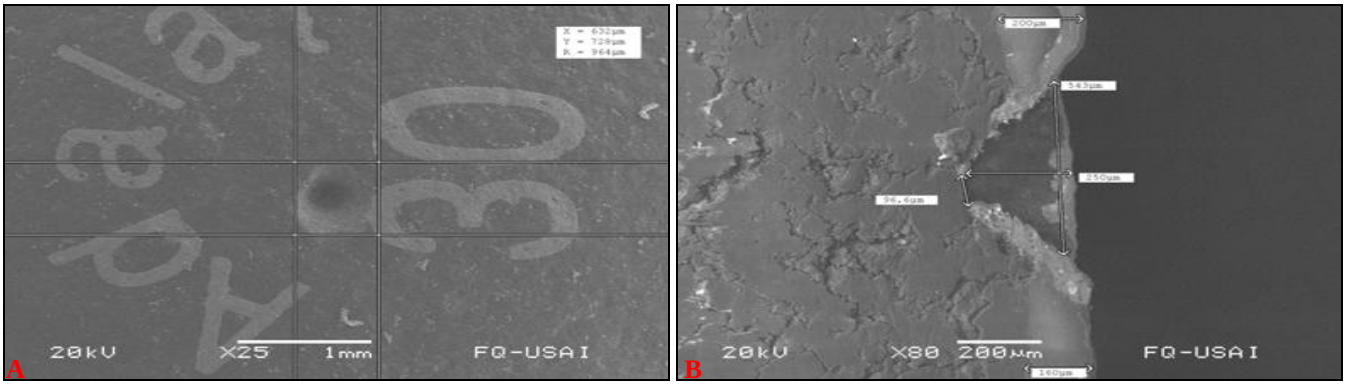

FIG. 3: MICROPHOTOGRAPHS A) CORRESPONDING TO THE SURFACE OF A TABLET OF THE ADALAT OROS® REFERENCE PRODUCT AND B) CORRESPONDING TO THE CROSS SECTION [12]

The average weight gain of coated tablets was 18.3%. The delivery orifices drilled on the pull layer of tablets were observed under a scanning microscope (Jeol JSM-59000 LV), and the average diameter was of 0.56 mm. It is worth mentioning that delivery orifices in the commercially available reference product drilled by laser beam show an approximate diameter of 0.6 mm **Fig. 2** and **3**.

Evaluation of Push-Pull Tablets:

Average Weight and Hardness: Table 3 summarizes the average weight and hardness exhibited by each batch of uncoated and coated tablets. The gain weight ranged from 18.48 to 20.91%, and the coating rendered mechanical resistance to the tablets, as evidenced by over two-fold force (kp) values for every coated tablet batch compared to the non-coated cores.

TABLE 3: VALUES OF HARDNESS AND AVERAGE WEIGHT OF BI-LAYER TABLETS AND PUSH-PULL TABLETS (n=10), SD: STANDARD DEVIATION

	Average weight (mg) + SD	Hardness (Kp) + SD
Bi-layer tablets Core	302.83 ± 4.13	20.70 ± 1.38
Push-pull tablets NSD	366.17 ± 9.22	49.95 ± 2.52
Push-pull tablets CPVP	364.48 ± 5.43	54.15 ± 2.15
Push-pull tablets CS	358.78 ± 3.61	50.35 ± 2.34
Push-pull tablets SSG	359.12 ± 3.44	51.14 ± 2.33

Dissolution Profile: In the specific case of Nifedipine, it has been reported that gastric and intestinal fluids or de-ionized water do not affect drug release from tablets prepared without super-disintegrants (NSD) [9]. In our study, we used a 0.05M phosphate buffer at pH 7.4 as dissolution medium since it has been reported that SD loses their disintegrating properties in acidic media [12, 13]. **Fig. 4** shows the drug release profiles of Nifedipine osmotic push-pull tablets elaborated with SD in the drug layer compared to those of the reference product (Adalat OROS®).

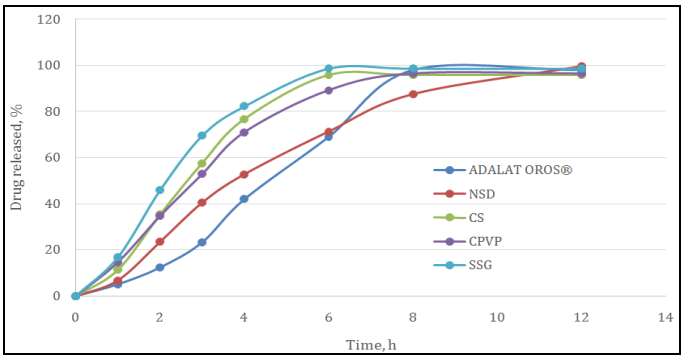

FIG. 4: RELEASE PROFILE OF NIFEDIPINE AT 12 h OF RELEASE OF ALL BATCHES ELABORATED AND COMPARED TO THE COMMERCIAL BATCH (n=6)

Fig. 4 showed that formulations with SSG, CS, and CPVP yielded faster releases of Nifedipine compared to the batch NSD, as well as to the commercially available reference product Adalat OROS®. However, the similarity factor (*f*2) showed that there were no differences in drug-release profiles comparing the different formulations to the reference product **Table 4**. The exception was the formulation containing SSG, since a value lower than 50 in the similarity factor means the release profiles are not similar.

TABLE 4: SIMILARITY FACTORS (*f*2) AT 6 AND 12 h OF ASSAY

Batches compared with Adalat OROS®	f_2 6 h	f_2 12 h
NSD	48.7	72.2
CPVP	31.1	57.3
CS	27.5	53.9
SSG	22.7	48.7

Furthermore, we observed differences in the first hour of the assay. Adalat OROS® and the formulations NSD had released 5% of the drug, whereas the formulation with CS, CPVP, and SSG had released 11%, 16%, and 16% of the drug, respectively. At 6 h of the assay, the formulations with CS and SSG had released practically 100% of the drug. It is important to mention that the aim of the present study was to show the influence of SD on the lag phase of osmotic tablets. Hence, **Table 5** shows the data of the first 6 h of drug release, including the lag time and initial release. The table shows that the formulations supplemented with SD had a significantly faster release rate at 6 h than the formulation NSD and the reference product Adalat OROS®. The results of the present study reveal that SD renders a rapid release of Nifedipine given the reduction in lag time. The addition of SD facilitates the faster contact of the drug with the dissolution medium, which leads to the disintegration of the matrix of the pull layer and enhances the force exerted by the push layer [14, 15].

TABLE 5: RELEASE RATE AND LATENCY TIME OF THE DIFFERENT BATCHES AT 6 h OF ASSAY

	Adalat OROS® (%)	NSD (%)	CS (%)	CPVP (%)	SSG (%)
Slop	13.23	12.88	16.93	15.01	15.95
y-intercept	11.95	2.21	1.19	4.51	11.62
R^2	0.984	0.9772	0.9578	0.9695	0.9161
T lag (h)	1	0.25	0	-0.5	-0.75
% Max.	68.88	71.33	95.76	89.3	98.7

Our results show that CPVP has a greater influence on the release rate than the other SD. CPVP is a non-ionic compound that avoids its interaction with cationic and insoluble drugs, such as Nifedipine. The superdisintegrants, CPVP, CS, and SSG, exhibit a wide range of intrinsic swelling properties (SSG>CS>>CPVP), but all of them are effective [14, 16]. Furthermore, CPVP exhibits another mechanism for its disintegrative function, namely strain recovery, which sustains that the porosity of tablets creates penetration routes for the fluids in the tablet. When the tablet is placed in an adequate aqueous medium, the medium penetrates replacing air found between the particles, in turn, weakening the intermolecular bonds and breaking up the tablet into finer particles. The amount of water captured by the tablet depends on how hydrophilic the drug/superdisintegrant is and the conditions of the matrix. The functioning of this type of SD requires maintenance of pore structure and low interfacial tension to the aqueous fluids since this helps create a hydrophilic environment surrounding the drug particles [14, 16].

Regarding the increase in release rates achieved by CS and SSG, some studies confirm that this SD greatly improves the solubility rate of Nifedipine. Ramana *et al*., report that the matrix tablets based on dispersions of NP in olibanum gum and methocel K4M, formulated with SSG and CS, showed a complete and faster release in a period of 12 h, following the kinetics of release of first-order compared to matrix tablets NSD [17].

Mahrous *et al*., studied the effect of three superdisintegrants; crospovidone, croscarmellose sodium, and sodium starch glycolate using ODTs of Clopidrogel, they reported that *in-vitro* disintegration tests and in vitro drug release, tablets showed a fast disintegration within seconds at pH 6.8 and more than 90% of the drug was released within 5 min in acidic medium [18].

TABLE 6: PAIRED-SAMPLES t-TABLE

	Paired Differences					
	Mean	Std. Deviation	Std. Error mean	t	df	Sig. (2-tailed)
Adalat - NSD	-6.633	7.630	3.115	-2.129	5	.086
Adalat - CPVP	-19.075	11.428	4.665	-4.088	5	.009
Adalat - CS	-21.450	14.876	6.073	-3.532	5	.017
Adalat - SSG	-27.058	17.745	7.244	-3.735	5	.014
NSD - CPVP	-12.441	7.094	2.896	-4.296	5	.008
NSD - CS	-14.816	11.033	4.504	-3.289	5	.022
NSD - SSG	-20.425	12.151	4.960	-4.117	5	.009

Results obtained for the similarity factor at 6 h of release revealed differences in the release profile of the assayed formulations compared to the reference product **Table 4**. For the tablets prepared NSD the

value of *f*2 was very close to 50 at 6 h, revealing a profile that is very similar to that of the reference product. However, since a value equal or higher to 50 is required to make a consideration of similarity with the reference product, we conducted a statistical analysis employing t-tests for paired samples to compare release profiles. Comparison of the release profiles of Adalat OROS® and the tablets NSD yields a P-value of 0.086, meaning no significant differences and concordant with the value close to 50 obtained in the similarity factor test. However, P-values of the t-test showed significant differences when comparing the release profiles of tablets elaborated with SD with the profiles of Adalat OROS® and the osmotic tablets NSD **Table 6**.

Influence on Lag Time: Lag time in drug release is frequently encountered in PPOSs. Garbacz *et al*., report that release of Nifedipine in the Adalat OROS® 30 mg formulation starts at the second hour, at which time the yield is below 10% of the active drug [10]. This increased lag time was also observed in the present study. Our results show that release started in the first hour and lag time was decreased using SD in the formulations, compared to the reference product and the tablets NSD. **Fig. 5** shows this performance; the formulations containing SD released more than 10% of Nifedipine in the first hour and up to 35% or more in the second hour of the assay. The addition of SD to osmotic systems may enhance the release rate of drugs and thus their bioavailability, which is particularly important in terms of the results published by Chung *et al*., who report that lag times of conventional Nifedipine tablets *in-vivo* (~6-24 h) are even greater than *in-vitro* (~2-20 h) [19]. However, it must be remembered that other factors influence lag time, including the size of the delivery orifice, pH, agitation rate in drug delivery, thickness of the membrane, osmotic agent and swelling polymers used [20, 21].

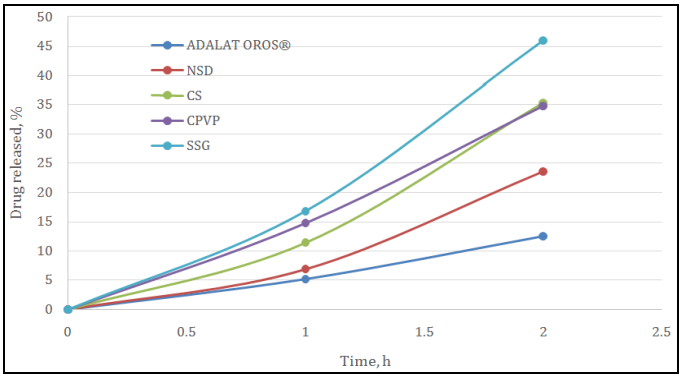

FIG. 5: RELEASE PROFILE OF NIFEDIPINE, WITH THE DIFFERENT SUPERDISINTEGRANTS USED (n = 6) AT FIRST TWO HOURS OF THE STUDY

Drug Release Kinetics: To determine the release kinetics of the drug, we calculated the value of R^2 at 6 h of an assay for each proposed kinetic model and selecting the best fit. Our results on release profiles of R^2 show that the system is best described by zero order kinetics, as compared to first order and Higuchi model kinetics **Table 7**.

TABLE 7: PARAMETERS OF THE RELEASE KINETICS MODELS CALCULATED AFTER 6 h OF ASSAY

	Zero-order		First order		Higuchi	
Parameters	**R^2**	**k**	**R^2**	**k**	**R^2**	**k**
Adalat OROS®	0.963	11.885	0.893	0.677	0.769	26.725
NSD	0.973	12.424	0.791	0.679	0.881	29.752
CS	0.979	17.482	0.736	0.686	0.901	42.205
CPVP	0.981	15.363	0.684	0.638	0.934	37.727
SSG	0.943	17.282	0.664	0.657	0.937	43.349

R^2: Determination coefficient; k: Release rate constants for the respective models.

The formulation containing CPVP was the most adequate for Nifedipine release as calculated by the R^2 value following zero order kinetics.

CONCLUSION: The use of SD in the drug layer of the push-pull osmotic tablets allowed reducing the lag time by increasing the release rate from the first hour onward and achieved a controlled release with zero-order kinetics. Adding superdisintegrants to the drug layer of push-pull osmotic tablets achieves a reduction in the lag time often encountered in this type of system. At the first hour, the tablets elaborated with SD had released over 10% of Nifedipine and over 35% in the second hour, compared to a 5 and 20% release by the reference product and the tablets NSD at 1 and 2 h, respectively.

The addition of CPVP, CS, and SSG in PPOSs is an important option when the drugs are poorly soluble since they show a noticeable increase of drug release rate as compared to tablets without SD

and the commercially available reference product Adalat OROS®. The release rate increased according to the SD added as follows: CPVP< CS< SSG. The similarity factor at 6 h of the assay for tablets NSD (48.7), tablets with CPVP (31.1), CS (27.5), and SSG (22.7) showed differences in the release profiles compared to the product of reference. However, a paired sample t-test statistical analysis revealed that there were no significant differences in the release profiles of Adalat OROS® compared to tablets NSD (P=0.086), whereas statistically significant differences were found in the release profiles of tablets elaborated with SD (P<0.05) Release kinetics analysis at 6 h of assay showed that all batches followed a zero-order equation, where the best fit was found for the tablets supplemented with CPVP rendering an R^2 value of 0.991.

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CONFLICT OF INTEREST: The authors declare no conflict of interest associated with this work.

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