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FORMULATION AND EVALUATION OF VINPOCETINE ORODISPERSIBLE TABLETS: *IN-VITRO* CHARACTERIZATION AND *IN-VIVO* PHARMACOKINETIC STUDY

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ABSTRACT: Objective: This research article aims to formulate and evaluate orodispersible tablets (ODTs) for Vinpocetine, a nootropic drug used for improving brain functions and cerebral blood flow. This will provide a convenient way for taking medication for dysphagia patients and therefore improve compliance. **Methods:** Vinpocetine ODTs were prepared by using superdisintegrants. A full mixed $3^1 \times 4^1$ factorial design was applied to evaluate the effect of two independent variables, namely superdisintegrant type (crospovidone, croscarmellose sodium and sodium starch glycolate) and superdisintegrant concentration (2.5, 5, 7.5, and 10%) on four responses namely friability, disintegration time, wetting time and dissolution percent after 5 min. Compatibility study was carried out using differential scanning calorimetry. Various physico-chemical properties were measured, and *in-vivo* pharmaco-kinetic study for a selected formula was performed against a conventional tablet market product. **Results:** Results showed that formulae ingredients were compatible. Crospovidone showed the shortest disintegration time and wetting time. Friability was less than 1%in all formulae, and dissolution percent after 5 min was greater than 80% in all formulae. Statistical evaluation of the results showed that tablets prepared by crospovidone showed the highest desirability value. The *in-vivo* study showed higher C_{max} and AUC of ODTs over conventional tablets. **Conclusion:** It can be concluded that vinpocetine ODTs can be successfully prepared using superdisintegrants, and the selected ODT formulation showed improved bioavailability compared to conventional tablet market product.

INTRODUCTION: Dysphagia or difficulty in swallowing is a relatively common condition and a major complaint among the elderly, yet it is a serious condition affecting the way of life that is currently described as a geriatric giant [1]. Dysphagia can be defined as any disruption in the swallowing process during bolus transport from the oral cavity to the stomach [2].

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The use of oral drug delivery is thus considered a big challenge for those suffering from dysphagia. Therefore orodispersible tablets dosage form is one of the most important solutions for such challenge, as it provides a convenient and easy way for drug administration by dysphagia patients [3].

Orodispersible tablets can be defined as "A solid dosage form containing medicinal substances which disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue" [4], and therefore it provides convenient dosing for patients with dysphagia. It has the advantages of both dry formulations through accurate dosing and ease of handling, and liquid formulations through the ease

of swallowing, and therefore it provides improved patient convenience and compliance [5].

Vinpocetine is a semi-synthetic derivative of vincamine; an alkaloid derived from *Vinca minor* L. plant. It is used for the treatment of cerebro-vascular and cognitive disorders, as it enhances brain functions and cognitive ability through increasing cerebral blood flow [6, 7]. Therefore, it is important to provide such an important drug, "vinpocetine" in a dosage form convenient for patients who will administer it.

In this research, orodispersible tablets of vinpocetine were prepared by direct compression procedure through the use of different types of superdisintegrants, at different concentration levels for each type, *in-vitro* and *in-vivo* studies were performed.

MATERIALS AND METHODS:

Materials: Vinpocetine was kindly provided by AlfaCure Pharmaceuticals. Pearlitol® Flash (compound of mannitol and starch) and Glycolys ® (sodium starch glycolate) were provided from Roquette, France. Prosolv® SMCC HD 90 (silicified microcrystalline cellulose) and Pruv® (sodium stearyl fumarate) were provided from JRS Pharma, Germany. Tablettose® 80 (agglomerated alpha-lactose monohydrate for direct compression) was from Meggle, Germany. Crospovidone was from Quzhou Jianhua Nanhang Industrial Co. Ltd., China. Disolcel® (croscarmellose sodium) was from Mingtai- Taiwan. Sucralose was from JK Sucralose Inc., China. Vanillin was from Luna Co. for Flavours & Fragrances, Egypt. Other materials were lab-grade materials.

Design of Experiment: A full mixed $3^1 \times 4^1$ factorial design was applied in order to study the effect of 2 independent variables namely superdisintegrant type (X1) and superdisintegrant concentration (X2) on the formulation of vinpocetine orodispersible tablets. X1 was studied at 3 levels where 3 different types of super-disintegrants were used, which were crospovidone, croscarmellose sodium and sodium starch glycolate. X2 was studied at 4 levels where 4 concentration levels were used for each super-disintegrant, which were 2.5%, 5%, 7.5%, and 10%. Experimental design and different levels are summarized in **Table 1**. The composition of different formulae is presented in **Table 2**. Four responses were selected for statistical evaluation which were friability (Y1), disintegration time, (Y2), wetting time (Y3), and dissolution percent after 5 min (Y4), where these responses resemble critical quality attributes of the formulations.

TABLE 1: EXPERIMENTAL DESIGN VARIABLES APPLIED FOR VINPOCETINE ODTs PREPARED BY SUPERDISINTEGRANTS

Variables	No. of levels	Levels			
Type of Superdisintegrant	3	Crospovidone	Croscarmellose Sodium	Sodium Starch Glycolate	
Concentration of Superdisintegrant	4	2.5%	5%	7.5%	10%

TABLE 2: TABLET COMPOSITION FOR DIFFERENT VINPOCETINE ODTs PREPARED BY SUPERDISINTEGRANTS

	Quantity / Tablet (mg)											
Raw Material	**FSD1**	**FSD2**	**FSD3**	**FSD4**	**FSD5**	**FSD6**	**FSD7**	**FSD8**	**FSD9**	**FSD10**	**FSD11**	**FSD12**
Vinpocetine	5	5	5	5	5	5	5	5	5	5	5	5
Pearlitol Flash	50	50	50	50	50	50	50	50	50	50	50	50
Silicified Microcrystalline Cellulose (Prosolv HD90)	50	50	50	50	50	50	50	50	50	50	50	50
Lactose monohydrate (Tablettose 80)	58.05	53.8	49.55	45.3	58.05	53.8	49.55	45.3	58.05	53.8	49.55	45.3
Crospovidone	4.25mg 2.5%	8.5mg 5%	12.75mg 7.5%	17 mg 10%	---	---	---	---	---	---	---	---
Croscarmelose Sodium	---	---	---	---	4.25mg 2.5%	8.5mg 5%	12.75mg 7.5%	17mg 10%	---	---	---	---
Sodium Starch Glycolate	---	---	---	---	---	---	---	---	4.25mg 2.5%	8.5mg 5%	12.75mg 7.5%	17mg 10%
Sucralose	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Vanillin	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sodium Stearyl Fumarate	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7
Total (mg)	170	170	170	170	170	170	170	170	170	170	170	170

Compatibility Study between Vinpocetine and Different Excipients Used:

Differential Scanning Calorimetry (DSC): Compatibility study between the active pharmaceutical ingredient (API) vinpocetine, and other excipients used was performed using DSC, where DSC thermograms were constructed for vinpocetine, used excipients, and selected formulations. Formulae with the highest concentrations of superdisintegrant were selected for the compatibility study, which were formulae no. FSD4, FSD8, and FSD12.

Formulae composition is presented in **Table 2**. DSC thermograms were prepared using a heating rate of 10 °C per minute, through a temperature range from 40 °C to 250 °C under nitrogen, with a nitrogen flow rate of 50ml per min.

Preparation of Vinpocetine Orodispersible Tablets using Different Superdisintegrants: Vinpocetine orodispersible tablets were prepared by dry mixing, direct compression process. Ingredients were mixed gradually with each other based on geometric dilution concept in the addition process to ensure good distribution of vinpocetine (API) within the blend [8]. The dry mixed powder was finally lubricated by sodium stearyl fumarate, and then the prepared powder blend was compressed using single punch compression machine, using round flat punch of 8 mm diameter.

***In-vitro* Characterization of the Prepared Formulae:**

Average Weight: Ten tablets randomly selected from each formulation were weighed individually. The individual weights and the total average weight were recorded and compared to the pharmacopeial limit of average weight, which is equal to ±7.5% of the theoretical weight [9, 10].

Hardness: Ten tablets were tested for hardness by a vanguard LIH-2 hardness tester. Tablets were placed between the two jaws of the hardness tester, where one of which is attached to a load cell and the other to a motor, which provides the mechanical drive. During testing, the motorized jaw drives forward, pressing the tablet against the fixed jaw until the tablet breaks. The load required to break the tablet is recorded and expressed in Kg force or Kilopond (Kp), and the average hardness was calculated [11].

Friability: Ten tablets were accurately weighed from each formula and placed in the drum of the friabilator. The tested tablets were rotated at 25 rpm for a period of 4 min, *i.e.,* tablets were subjected to 100 rotations. Tablets were then reweighed, and the percentage loss in weight was calculated and taken as a measure of friability by the following equation.

Friability % = (Initial weight- Final weight) / (Initial weight) × 100 [12]

Disintegration Time: The disintegration time test was performed by placing 6 tablets in the disintegration apparatus. The immersion fluid used was water at temperature 37 ± 2 °C. The disintegration tester was operated, and the time taken for the complete disintegration of the tablet was recorded in seconds [10, 13].

Wetting Time: The wetting time test was performed by arranging five circular tissue papers in a petridish of 9 cm diameter. To this petridish, 9 ml of water containing amaranth (a water-soluble dye) was poured to provide red-colored wet surface. Tablets were then placed on the surface of the tissue paper, and the time required for water to reach the upper surface of the tablet was recorded in seconds as the tablet wetting time [14].

Determination of Drug Content: The drug content of the powder mixture was measured by accurately weighing170 mg of the tablet powder (containing 5 mg vinpocetine). This weight was properly dissolved and sonicated with methanol to 50 ml, then filtered through filter paper no. 41, and 10 ml of the filtrate was withdrawn and diluted to 50 ml with methanol to reach a final concentration of 20mcg/ml. The final dilution was measured using a UV/VIS spectrophotometer (hp Hewlett Packard 8452A) at λ_{max} of 274 nm [15]. A powder mixture without the API prepared and treated by the same conditions was used as a blank to avoid interference from formula components, if any [16].

***In-vitro* Dissolution of Vinpocetine from Prepared Orodispersible Tablets:** The dissolution of vinpocetine from the prepared orodispersible tablets was evaluated using USP Apparatus II (Paddle method). The rotation speed was set as 50 rpm [17]. The dissolution medium used was 0.1 N HCl.

The volume of the dissolution medium was 500 ml in each dissolution vessel [18]. The temperature of the dissolution medium was adjusted to 37 ± 0.5 °C [18]. Aliquots of 5 ml were withdrawn from each vessel at time intervals of 5, 10, 15 & 20 min, and were replaced with fresh media. The withdrawn samples were filtered through filter paper no. 41, and the filtrate was measured using UV/VIS spectro-photometer (hp Hewlett Packard 8452A) at λ_{max} of 274 nm [15]. A tablet without the API prepared and treated by the same conditions was used as a blank, to avoid interference from formula components if any [16].

Statistical Evaluation of the Results and Best Formula Selection:

ANOVA Testing and Statistical Analysis: Statistical analysis was implemented using Design Expert® software. A statistical analysis using one-way ANOVA test was performed to detect the significance of the model terms or formula variables. A model term is considered significant if the p-value is less than 0.05 [19, 20, 21]. Response graphs were plotted for the tested variables.

Desirability Value Measurement and Selection of the Best Formula: Design Expert® software was used to choose the best formula based on the desirability value calculated. Desirability is an objective function ranging from zero to one (least to most desirable, respectively). The goals were set to have the lowest disintegration time, lowest wetting time, highest dissolution percent after 5 min and lowest friability percent. Desirability value was calculated for the combined factors together. The optimized formulation was chosen based on the desirability value [22].

Further Characterization of the Selected Formula:

Differential Scanning Calorimetry: Differential scanning calorimetry was performed for the 2 formulations having the highest desirability values . DSC was performed as explained in section 2.3.1.

***In-vivo* Pharmacokinetic Study of the Selected Formula:**

Study Design: The most desirable formula was selected for further study for its pharmacokinetics against conventional tablet market products (Vinporal®, Amriya Pharmaceuticals, Egypt). The experiment was approved by the Research Ethics Committee, Faculty of Pharmacy, Cairo University. The study was a parallel design in which six healthy New Zealand male rabbits weighing 2.5Kg ± 0.5Kg [23] were randomly divided into two groups of equal size; each group consisted of three rabbits [24]. Animals were kept one week for adaptation prior to conducting the experiment [25]. Animals were fasted overnight with free access to water before dosing [26]. Group (I) received a dose of 10 mg/kg of vinpocetine from vinpocetine ODT formula FSD1 (the most desirable formula). Group (II) received a dose of 10 mg/kg of vinpocetine from Vinporal® tablets (a marketed conventional tablet dosage form for vinpocetine). Blood samples collection were done through modified technique for orbital sinus sampling [27, 28, 29]. Blood was collected into heparinized glass tubes. Plasma was obtained by centrifugation of collected blood samples at 4000 rpm for 15 min. Samples were freezed until analysis and were collected at time intervals of 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 h after drug administration [26].

Sample Preparation: A plasma sample of 200µL was transferred into a test tube, 50 µL of internal standard (IS: Torsemide) working solution (500 ng/ml) was added to it, and vortexed for10 seconds, then 4ml of ethyl acetate was added to each sample, vortexed for 3 min and centrifuged for 10 min at 4000 rpm. The organic layer was transferred into another tube and evaporated to dryness using a centrifugal vacuum concentrator at 60 ℃. Dry residues were then reconstituted in 200µL of mobile phase and vortexed for 1 min.

Chromatographic Conditions: A sensitive, selective, and accurate LC-MS/MS method was used for detection of vinpocetine in rabbit plasma 23.A Shimadzu LC system was used to inject 10 µL of the processed samples into Agilent C-18 column 50 mm × 50 mm × 5 µm diameter. The column temperature was maintained at room temperature. The isocratic mobile phase consisted of acetonitrile and water at a ratio of 80:20, respectively, with 0.1% v/v formic acid added to the mobile phase. The mobile phase was filtered, degassed, and delivered at a flow rate of 1 ml/minute into the mass spectrometer's electro-spray ionization chamber. 10 µL was injected using an autosampler. MS/MS detection was in positive ion mode. The mass spectrometer was equipped with a turbo ion spray interface at 400 °C. The ion

spray voltage was set at 5500 V. The common parameters, curtain gas, nebulizing gas, drying gas, and collision gas, were set at 10 psi, 18 psi, 40 psi, and 9 psi, respectively. The de-clustering potential and collision energies were 26V & 89V respectively for vinpocetine and 46V & 25V respectively for IS Torsemide.

The entrance potential was 10V, and the collision exit potential was 10V.

Multiple reaction monitoring (MRM) mode detections of the ions was performed in monitoring the transition of the m/z 351.672 precursor ion to the m/z 204.600 for vinpocetine and m/z 348.571 precursor ion to the m/z 263.80 for IS torsemide. The dwell time was 150msec for both vinpocetine and IS torsemide [30, 31, 32].

Pharmacokinetic Data Analysis and Bioavailability Evaluation: Pharmacokinetic parameters determined from vinpocetine plasma concentrations were calculated using "PKSolver" program, using non-compartmental analysis by linear trapezoidal method [23, 33]. Determined pharmacokinetic parameters were: C_{max}: the highest drug concentration during the study period, T_{max}: time taken to reach C_{max}, $AUC_{0-\infty}$: area under the plasma concentration time curve from time zero to infinity, $t_{1/2}$: half-life of elimination of vinpocetine, λz: terminal elimination rate constant, and $MRT_{0-\infty}$: Mean residence time.

RESULTS AND DISCUSSION:

Compatibility Study – Differential Scanning Calorimetry (DSC): DSC is a kind of thermal analysis that has been widely used for drug-excipients compatibility studies. It is a fast method for evaluating physicochemical interactions between drug and excipients [34]. The DSC thermograms of pure vinpocetine, excipients used, and selected formulations (FSD4, FSD8, and FSD12) were analyzed. DSC thermograms are presented in **Fig. 1**. Vinpocetine showed a sharp endothermic peak at about 151 ℃. Pearlitol Flash, sucralose, vanillin, and sodium stearyl fumarate showed endothermic peaks at 167 ℃, 122 ℃, 82 ℃, and 200 ℃ respectively. Lactose monohydrate (Tablettose80) showed two endothermic peaks at 142 ℃ and 218 ℃. Prosolv HD90, crospovidone, croscarmellose sodium, and sodium starch glycolate showed no peaks. The formulations tested FSD4, FSD8 and FSD12 revealed the persistence of the drug endothermic peak, yet with decreased intensity, and this may be attributed to the proportionality of the drug within the blend [35]. The persistence of the vinpocetine peak indicates that the formula ingredients are compatible with the drug.

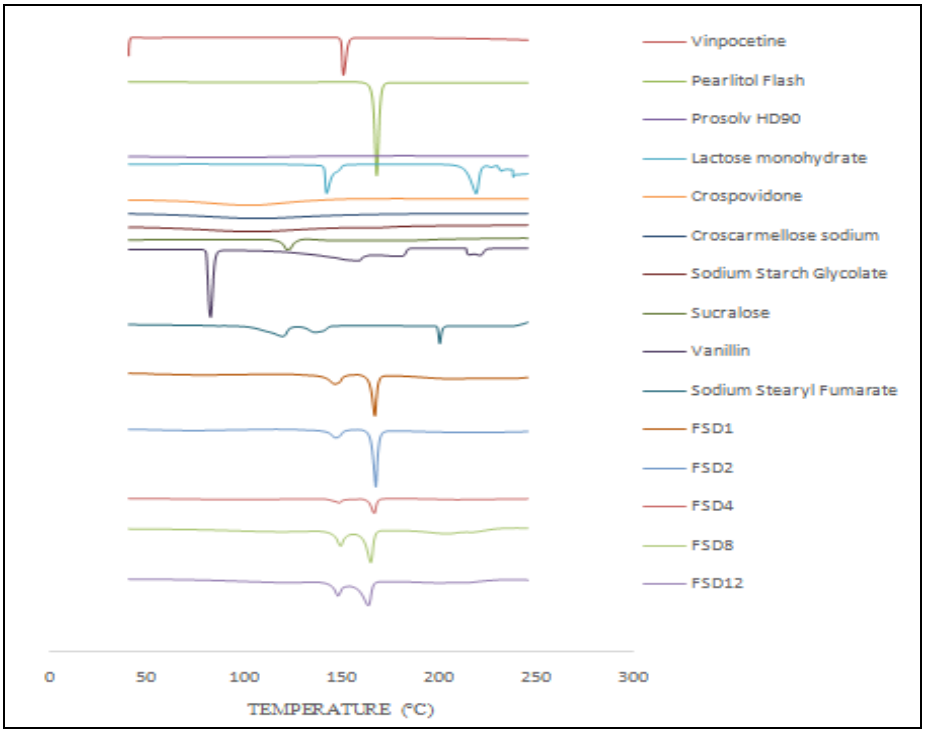

FIG. 1: DSC THERMOGRAMS OF VINPOCETINE, USED EXCIPIENTS, AND DIFFERENT FORMULATIONS

Average Weight: The theoretical weight of the tablet in all preparations was 170 mg. For this tablet weight, the limit of tablet weight should be within ± 7.5% of the theoretical weight according to British Pharmacopoeia (BP) limits. The results showed that all the preparations were within the acceptable official BP limit with a minimum of 170.61mg and a maximum of 174.67 mg as presented in **Table 3**. The results showed good uniformity of weight.

TABLE 3: RESULTS OF AVERAGE WEIGHT, HARDNESS, FRIABILITY, DISINTEGRATION TIME, WETTING TIME AND DRUG CONTENT

Formula	Average Weight (mg) ± SD	Hardness (KP) ± SD	Friability %	Disintegration Time (seconds) ± SD	Wetting Time (seconds)	Drug Content (%)± SD
FSD1	171.73 ±2.176	5.534± 0.841	0.37	18.5 ± 2.12	28	102.099± 0.012
FSD2	173.28 ±2.074	4.398± 0.589	0.4	15 ± 1.414	25	103.277± 0.142
FSD3	173.6 ±1.957	5.168± 0.839	0.4	16± 0	22	104.033± 0.170
FSD4	172.4 ± 1.963	4.984± 1.191	0.57	16± 0	20	99.184± 0.201
FSD5	173.53 ± 1.359	4.212± 0.651	0.31	20± 1.414	46	95.85± 0.149
FSD6	170.61 ± 1.762	4.382± 0.455	0.38	27.5± 0.707	48	92.93± 0.221
FSD7	173.14 ± 2.200	4.458± 0.614	0.44	30± 1.414	54	94.59± 0.065
FSD8	174.67 ± 2.466	4.266± 0.462	0.52	37± 0	67	93.52± 0.006
FSD9	172.4 ± 1.476	4.894± 1.217	0.52	19.5± 0.707	31	97.68± 0.013
FSD10	173.29 ± 1.042	4.464± 0.614	0.57	20.5± 0.707	40	94.46± 0.154
FSD11	173.05 ± 1.587	4.554± 0.637	0.59	30± 4.243	52	94.28± 0.024
FSD12	173.67 ± 1.896	5.46± 0.776	0.59	30± 5.657	62	90.24± 0.218

Hardness: Tablet hardness of ODT formulations should be adjusted carefully in order to have sufficient mechanical strength for tablets to withstand handling, yet without exerting excessive pressure, which can retard tablet disintegration [36]. The tablet's hardness during compression was adjusted in order to keep this balance. The average hardness results of the tested formulations ranged from 4.212 Kp to 5.534 Kp, and these results were considered acceptable, where the tablets showed acceptable mechanical strength without adverse effect on the disintegration time. Hardness results are presented in **Table 3**.

Friability: Friability is the tendency for a tablet to chip or break after compression. The friability of orodispersible tablets is one of the critical parameters because many orodispersible tablets suffer from poor friability. In this study, results ranged from 0.31% minimum to 0.59% maximum. These results comply with the official BP limits, where friability percent should be not greater than 1% [10]. Tablets were considered within the acceptable range for all formulae as presented in **Table 3**, which indicates the good mechanical strength of the tablets.

ANOVA testing for friability response was done. It was found that the p-value of both type of super-disintegrant and concentration of superdisintegrant were less than 0.05, as explained in **Table 4**, which indicates that both type and concentration of superdisintegrant are significant model terms.

The results of the factorial study are graphed in **Fig. 2** and **Fig. 3**. The graphs showed that the lowest friability percent was exhibited by the formulae prepared with croscarmellose sodium [37], while friability of formulae prepared with sodium starch glycolate showed the highest friability percent values. It was also found that there is a direct relationship between the concentration level of superdisintegrant, and the friability percent.

The final equation in terms of coded factors was as follows:

Friability = +0.4717 -0.0367A[1] -0.0592A[2] -0.0717B[1] -0.0217B[2] +0.0050 B[3]

Where +0.4717 is the coefficient of the intercept or the overall grand average response of all the runs. The other coefficients estimates represent the expected change in response per unit change in factor value when all remaining factors are held constant. (A) is the independent factor of the type of superdisintegrant. A[1] and A[2] are the crospovidone level and the croscarmellose sodium level of the type of superdisintegrant factor, respectively. (B) is the independent factor of concentration of superdisintegrant. B[1], B[2] and B[3] are the 2.5%, 5% and 7.5% concentration levels of concentration of superdisintegrant factor

respectively. The last level is not included in the equation and is calculated mathematically as the difference between the grand average and the average at each level.

The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients. From the friability response equation, we can understand that the friability was low when we used crospovidone as declared by the negative value of the coefficient of A[1], and was more lowered when the type of superdisintegrant was changed to croscarmellose sodium as declared by the negative value of the coefficient of A[2], and was increased by using sodium starch glycolate as can be mathematically calculated by the difference between the grand average (coefficient of intercept) and the average at each level.

Regarding the other factor (B) - which is the concentration of superdisintegrant - the friability was the lowest at the 2.5% concentration level, followed by 5% concentration level as indicated by the negative values, then the friability increased at the 7.5% concentration level as indicated by the positive value and was the highest at the 10% concentration level calculated by the difference between the grand average (coefficient of intercept) and the average at each level.

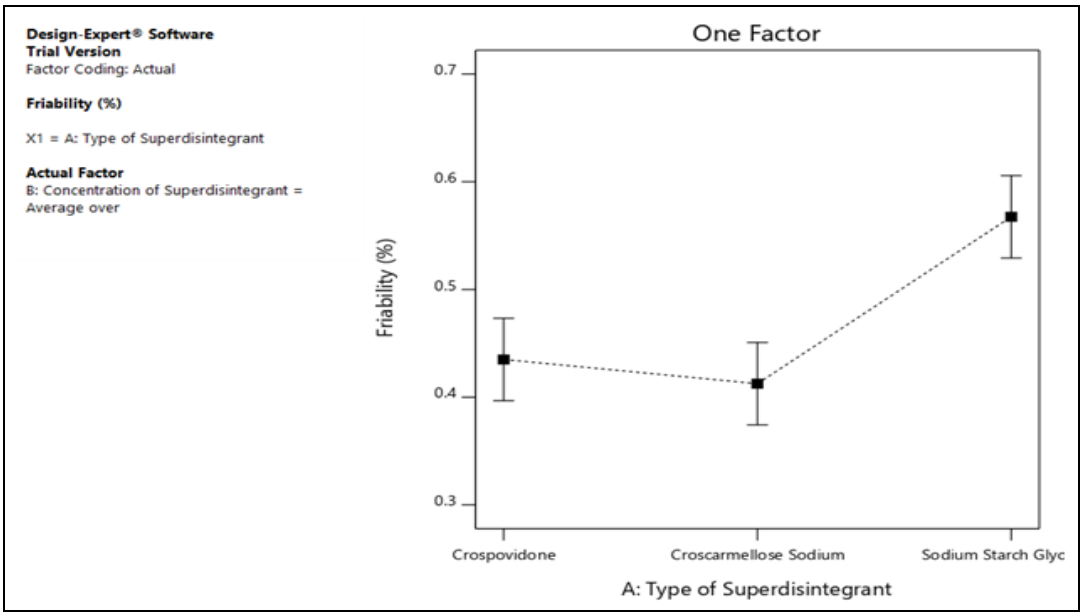

FIG. 2: AVERAGE FRIABILITY PERCENT FOR DIFFERENT TYPES OF SUPERDISINTEGRANT

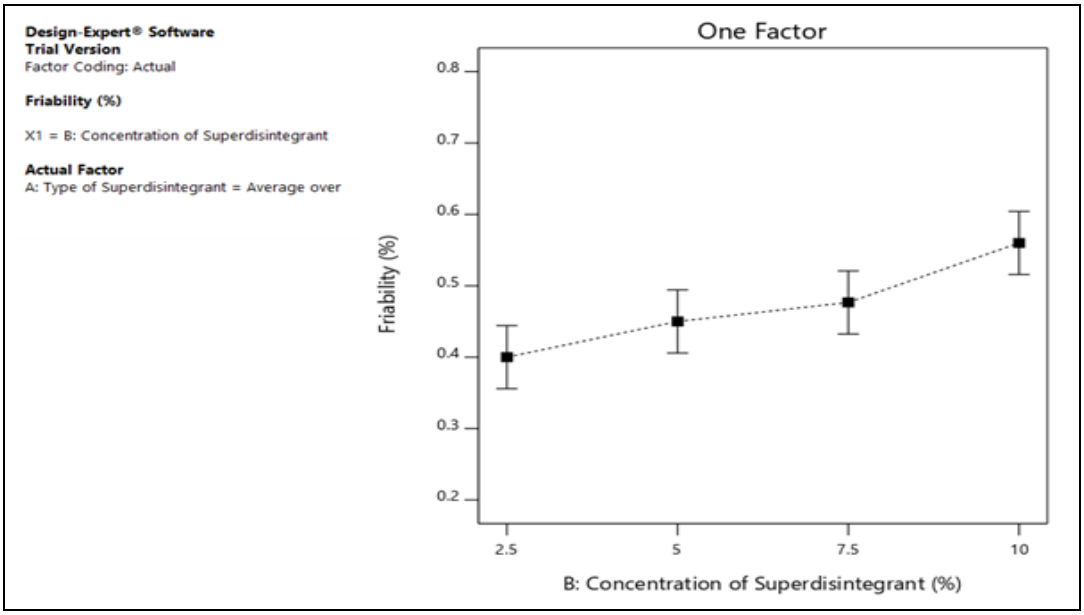

FIG. 3: AVERAGE FRIABILITY PERCENT FOR DIFFERENT CONCENTRATIONS OF SUPERDISINTEGRANT

TABLE 4: ANOVA P-VALUES FOR SELECTED PARAMETERS

Source	p-value Disintegration	p-value Wetting Time	p-value Dissolution percent after 5 min	p-value Friability
Model	0.0729	0.0273	0.3952	0.0074
A-Type of Superdisintegrant	0.0328	0.0079	0.2814	0.0052
B-Concentration of Superdisintegrant	0.2390	0.2968	0.4502	0.0229

Disintegration Time: Disintegration time is the most critical parameter of orodispersible tablets, as clear from the dosage form name which is orally disintegrating tablet. Other names of the dosage form are quick-dissolving tablets or fast-dissolving tablets denote that disintegration should be rapid enough to facilitate swallowing and consequently improve compliance, as this is the target of the formulation [37]. The disintegration limit of ODTs according to BP is set to be of a maximum of 3 min [10], while the FDA guidance for industry for orally disintegrating tablets recommends 30 sec or less [4].

The results of disintegration time for all preparations were ranging from 16 sec to 37 sec as presented in **Table 3**, which indicates proper rapid disintegration time for all formulations, yet crospovidone formulations were superior in showing the shortest disintegration time over other superdisintegrants used.

ANOVA testing for disintegration time response was performed. It was found that the p-value of the type of superdisintegrant was less than 0.05, which indicates that it is a significant model term rather than the concentration of the superdisintegrant as presented in **Table 4**. The graphs showed that the average disintegration time was the shortest with crospovidone, followed by sodium starch glycolate and croscarmellose sodium, respectively. A graphical illustration is presented in **Fig. 4**.

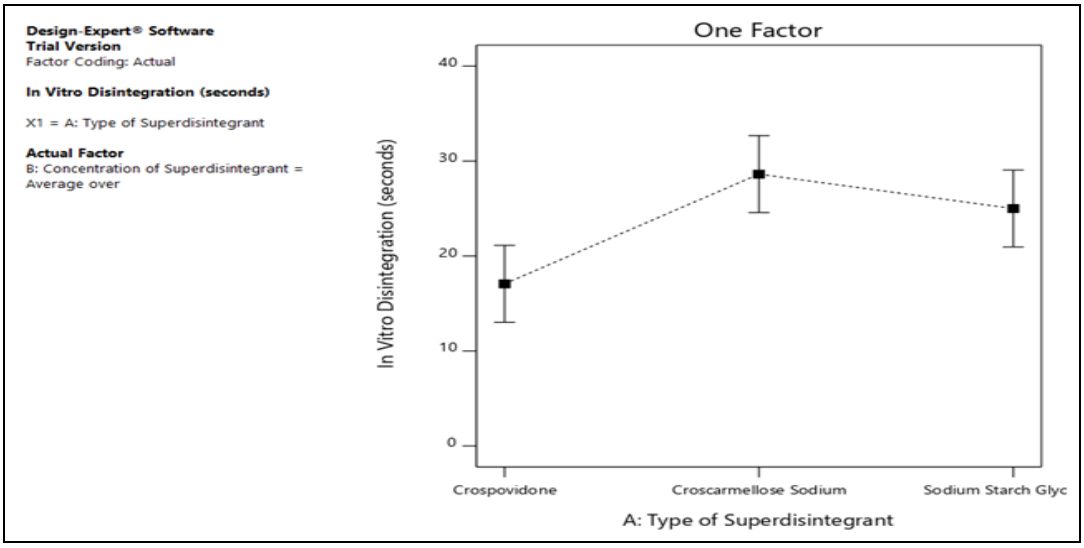

FIG. 4: AVERAGE DISINTEGRATION TIME FOR DIFFERENT SUPERDISINTEGRANT TYPES

This efficacy of crospovidone over other super-disintegrants could be attributed to the that it acts by both wicking and swelling mechanisms, where its porous structure facilitates wicking of liquid into the tablets, in addition to its high crosslinking, which allows rapid swelling in water without gel formation.

These criteria allowed it to show the best superdisintegrant performance for ODTs over croscarmellose sodium and sodium starch glycolate [38, 39].

The final equation in terms of coded factors was as follows:

Disintegration = +23.57-6.49A[1] +5.06 A[2] -4.23 B[1] -1.63 B[2] +1.77 B[3]

The equation terms are explained in the friability section in the results & discussion. From the disintegration equation, we can conclude that the shortest disintegration time was shown by crospovidone as indicated by the small negative co-efficient value of A[1].

The disintegration time increased by applying either croscarmellose sodium as indicated by the positive value of (A2) or sodium starch glycolate as mathematically calculated.

The disintegration time was low at the concentration levels of 2.5% and 5% as indicated by the negative values of coefficients of B[1] and B[2], respectively, and the disintegration time increased by the increase of the concentration level of superdisintegrant to 7.5% and 10% as indicated by the positive value of the coefficient of B[3] and as mathematically calculated for the 10% concentration level.

Wetting Time: The wetting time refers to the ability of tablets to absorb water, which in turn eases the disintegration process [40]. The wetting time test is different from the disintegration time test in that it uses minimal water. It mimics tablets wetting by saliva, and therefore it could be more representative of reality [40, 16]. The wetting time of the tested formulae ranged from 20 sec to 67 sec as presented in **Table 3**. The shortest wetting time was exhibited by formulations prepared with crospovidone, which also showed the shortest disintegration time; and this could be explained by the wicking and swelling mechanism of crospovidone as explained in the disintegration time section in the results and discussion [39]. It is noteworthy that there is a direct relationship between disintegration time and wetting time, *i.e.* increasing the disintegration time increases the wetting time and *vice versa*. This is because both disintegration and wetting times are affected by tablet behaviour in water.

ANOVA testing for wetting time was performed, it was found that the p-value of the type of superdisintegrant was less than 0.05, which indicates that it is a significant model term rather than the concentration of the superdisintegrant. The p-values are summarized in **Table 4**, and the average results graph is presented in **Fig. 5**. The graph showed that crospovidone got the shortest wetting time, followed by sodium starch glycolate and croscarmellose sodium, respectively.

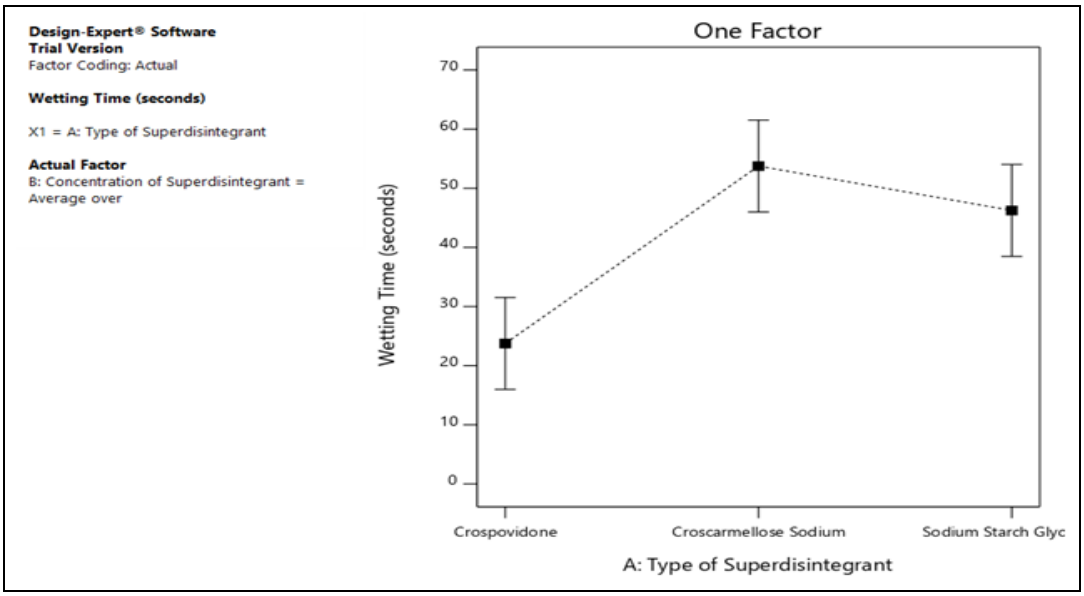

FIG. 5: AVERAGE WETTING TIME FOR DIFFERENT SUPERDISINTEGRANT TYPES

The final equation in terms of coded factors was as follows:

Wetting Time = +41.25 -17.50 A[1] +12.50 A[2] -6.25 B[1] -3.58 B[2] +1.42 B[3]

The equation terms are explained in the friability section in the results & discussion. From the wetting time equation, we can conclude that the wetting time was the shortest with crospovidone as indicated by the negative value of the coefficient of A[1], and it increased upon using croscarmellose sodium and sodium starch glycolate as indicated by the positive value for the coefficient of A[2] and as calculated mathematically for the sodium starch glycolate. The equation also declares that the wetting time was low with the 2.5% and 5% concentration levels as indicated by the negative coefficient values of B[1] and B[2] respectively,

and the wetting time increased by increasing the concentration level of super-disintegrant to 7.5% and 10% as indicated by the positive values for B[3] and as mathematically calculated for the 10% level of superdisintegrant.

Determination of Drug Content: Drug content is considered acceptable in the range from 90 to 110% [41]. The drug content results for all preparations were complying to this range. The results were ranging from 90.24% to 104.033% as presented in **Table 3**. All results were considered within the acceptable range, which indicates proper active ingredient dose within the blend.

***In-vitro* Dissolution of Vinpocetine from Prepared Orodispersible Tablets:** Dissolution is defined as the process by which solid substances enter into solvent to yield a solution or the process by which a solid substance dissolves [42]. Dissolution testing showed good dissolution results. After 5 min, the dissolution percent was above 80% for all formulae, while after 20 min, dissolution percent ranged from 84.42% to 102.57%. The formulations prepared with either sodium starch glycolate or crospovidone showed higher dissolution results than those prepared with croscarmellose sodium. Results of the dissolution profile are tabulated in **Table 5,** and corresponding graphs are presented in **Fig. 6**.

ANOVA testing for dissolution percent after 5minutes was done. From the ANOVA table, it was found that the p-value of both type of super-disintegrant and concentration of superdisintegrant was greater than 0.05, which indicates that the model terms are insignificant. p-values are summarized in **Table 4**. All results were considered within the acceptable range.

TABLE 5: DISSOLUTION PROFILE RESULTS

Formula	Dissolution Percent ± SD			
	5 min	10 min	15 min	20 min
FSD1	94.62±0.015	96.49± 0.006	96.94±0.015	97.51±0.013
FSD2	95.43±0.007	96.80±0.006	96.98±0.009	97.00±0.002
FSD3	93.55±0.011	95.48±0.005	95.83±0.005	96.79±0.004
FSD4	82.78±0.004	86.42±0.011	88.07±0.003	90.59±0.011
FSD5	90.76±0.002	99.25±0.025	99.61±0.003	100.67±0.010
FSD6	88.38±0.013	89.00±0.004	95.64±0.009	97.05±0.015
FSD7	82.44±0.001	82.80±0.008	83.25±0.008	84.42±0.001
FSD8	86.69±0.017	89.87±0.006	90.54±0.013	90.66±0.001
FSD9	91.29±0.020	102.47±0.017	102.52±0.012	102.57±0.009
FSD10	95.21±0.009	98.69±0.018	101.39±0.008	101.58±0.008
FSD11	87.31±0.007	87.42±0.010	91.42±0.008	92.47±0.010
FSD12	95.70±0.009	97.71±0.015	98.18±0.016	98.30±0.011

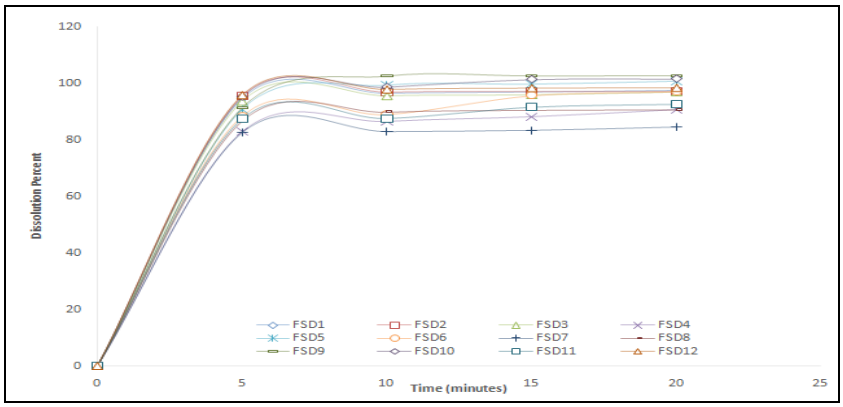

FIG. 6: DISSOLUTION PROFILE FOR VINPOCETINE ODTS PREPARED BY SUPERDISINTEGRANTS

The final equation in terms of coded factors was as follows:

Dissolution Percent after 5 minutes = +90.35 +1.25 A[1] -3.28 A[2] +1.88B[1] +2.66 B[2] -2.58 B[3]

From the equation, we can conclude that the dissolution percent after 5 min was increased by using crospovidone as indicated by the positive value of the coefficient of A[1] and was decreased

by the use of croscarmellose sodium as indicated by the negative value of the coefficient of A[2], and was increased by using sodium starch glycolate, as mathematically calculated. At 2.5% and 5% concentration levels of superdisintegrant, the dissolution percent was increased as indicated by the positive value of the coefficients of B[1] and B[2], respectively, and was decreased at the higher levels of superdisintegrant as indicated by the negative coefficient value of B[3] for the 7.5% concentration level, and as mathematically calculated for the 10% concentration level.

This drop observed at the initial 5 min dissolution results by the increase of the level of superdisintegrant could be attributed to the possible gelling that can occur with high levels of super-disintegrant.

Statistical Evaluation of the Results and Best Formula Selection: The effect of the two factors superdisintegrant type and superdisintegrant concentration on friability, disintegration time, wetting time, and dissolution percent after 5 min was studied; and the responses to these variables were considered in the best formula selection. The best formula was selected by Design Expert® software, based on the desirability value. The desirability approach assigns a score to a set of responses and chooses factor settings that maximize that score. The desirability values of the prepared formulae are presented in **Table 6**.

TABLE 6: DESIRABILITY VALUES FOR FORMULAE

Number	Formula no.	Desirability
1	FSD1	0.853
2	FSD2	0.850
3	FSD3	0.680
4	FSD9	0.668
5	FSD10	0.617
6	FSD4	0.617
7	FSD5	0.533
8	FSD6	0.489
9	FSD11	0.467
10	FSD12	0.378
11	FSD7	0.291
12	FSD8	0.214

The highest desirability value was for FSD1 which contains crospovidone superdisintegrant at 2.5% concentration level, followed by FSD2 which contains 5% crospovidone. These results indicate that crospovidone got the best performance as a superdisintegrant in orodispersible tablets formulation. It got the shortest disintegration and wetting time through its wicking and swelling mechanisms, and it showed the highest desirability values.

Further Characterization of the Selected Formula: Differential Scanning Calorimetry: The highest desirability formulations FSD1 and FSD2 were further analyzed by DSC to check the compatibility with the used excipients. Results showed that the drug peak was persistent indicating that the formula ingredients were compatible. DSC thermograms are presented in **Fig. 1**. The formulations tested FSD1 and FSD2 revealed the persistence of the drug endothermic peak, yet with decreased intensity and this may be attributed to the proportionality of the drug within the blend [35]. The persistence of the vinpocetine peak indicates that the formula ingredients are compatible with the drug.

***In-vivo* Pharmacokinetic Study of Selected Formula:** In-vivo pharmacokinetic study was performed to the most desirable formula FSD1 against conventional tablet market product (Vinporal® Tablets). The study purpose was to determine the difference between ODT dosage form and conventional oral tablets dosage form pharmacokinetics. After oral administration of both vinpocetine ODT FSD1 and Vinporal® tablets; it was found that C_{max} of the orodipsesible tablets was higher than that of Vinporal® tablets, as the results were 117.463 ± 34.043, and 94.804 ± 23.139 ng/ml respectively meaning that oro-dispersible tablets formula was about 1.24 folds higher than conventional tablets in the C_{max}, despite having the same t_{max} which was 0.5 h [43]. The mean residence time $MRT_{0-\infty}$ of vinpocetine ODT FSD1 was higher than that of Vinporal® tablets as the results were 3.635 ± 0.137 and 2.948 ± 0.199 hr, respectively. The $AUC_{0-\infty}$ for vinpocetine ODT FSD1 was higher than that of Vinporal® tablets as the results were 356.147 ± 58.850 and 222.569 ± 57.798 ng/ml*h respectively meaning that oro-dispersible tablets formula was about 1.6 folds higher than conventional tablets in AUC. The relative bioavailability of vinpocetine ODT FSD1 related to Vinporal® tablets (conventional tablets) was found to be 160.016 % *i.e.,* 1.6 fold higher than the conventional commercial tablets.

Mean plasma concentration results are presented in **Table 7**, graphed in **Fig. 7**, and pharmacokinetic results are presented in **Table 8**.

The increased C_{max}, AUC, and MRT0-∞ values of orodispersible tablets could be attributed to the possible pre-gastric absorption that can occur in the buccal cavity allowing for improved bioavailability [44]. From the results, it can be concluded that incorporating vinpocetine in the orodispersible tablet formula can improve and enhance the product bioavailability and can show improved pharmacokinetic results over that of conventional tablets.

TABLE 7: MEAN PLASMA CONCENTRATION OF VINPOCETINE ODT AND MARKET PRODUCT

Time (hr)	Vinpocetine ODT FSD1 Mean Plasma Concentration ± SD	Vinporal® Tablets Mean Plasma Concentration ± SD
0.25	21.518 ± 10.278	8.507 ± 3.272
0.5	117.463 ± 34.043	94.804 ± 23.139
1	83.125 ± 7.760	73.908 ± 16.616
1.5	72.930 ± 9.943	53.560 ± 17.330
2	61.655 ± 11.480	36.584 ± 7.892
3	44.059 ± 11.720	24.397 ± 8.516
4	31.028 ± 12.326	20.868 ± 5.038
6	23.535 ± 3.821	9.761 ± 3.083
8	10.153 ± 1.015	2.217 ± 3.839

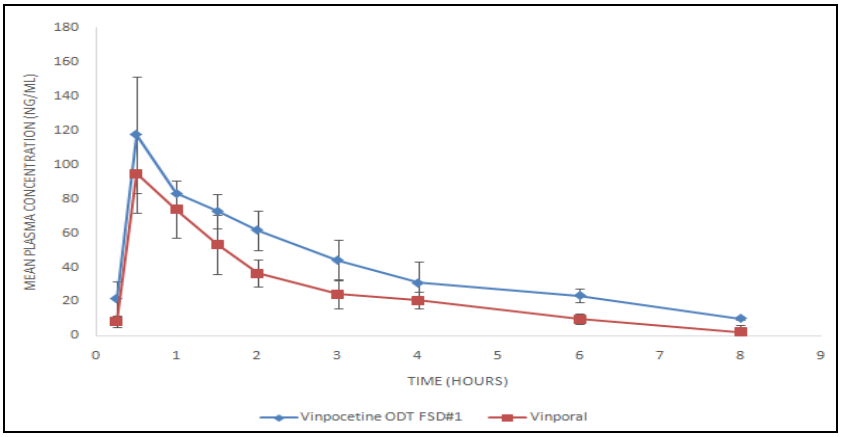

FIG. 7: MEAN PLASMA CONCENTRATION (ng/ml) – TIME (hr) PROFILE OF VINPOCETINE AFTER ORAL ADMINISTRATION OF VINPOCETINE ODT FSD1 AND VINPORAL® TABLETS

TABLE 8: MEAN PHARMACOKINETICS PARAMETERS OF VINPOCETINE FOLLOWING ORAL ADMINISTRATION OF VINPOCETINE ODT FSD1 AND VINPORAL® TABLETS

Parameter	Unit	ODT Tablets Mean Value ± SD	Vinporal® Tablets Mean value ± SD
λ_z	1/h	0.293 ± 0.005	0.351 ± 0.056
t1/2	h	2.364 ± 0.040	2.009 ± 0.297
T_{max}	h	0.500 ± 0.000	0.500 ± 0.000
C_{max}	ng/ml	117.463 ± 34.043	94.804 ± 23.139
$AUC_{0-\infty}$	ng/ml*h	356.147 ± 58.850	222.569 ± 57.798
$MRT_{0-\infty}$	h	3.635 ± 0.137	2.948 ± 0.199

CONCLUSION: Orodispersible tablets of vinpocetine were prepared by direct compression method through the use of different super-disintegrants, namely crospovidone, croscarmellose sodium and sodium starch glycolate at different concentrations. It was found that crospovidone showed the shortest disintegration time and the shortest wetting time compared to other super-disintegrants used. All formulations showed acceptable hardness and friability results. Dissolution results were acceptable in all preparations. Statistical evaluation was performed for all formulations, and the desirability value was calculated. It was found that the highest desirability value was for the formula prepared by 2.5% crospovidone, showing that crospovidne was superior in its results over other superdisintegrants applied. The most desirable formula was further subjected to an *in-vivo* pharmacokinetic study against conventional tablet market product, and it was found that orodispersible tablets showed enhanced bioavailability over conventional tablets.

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REFERENCES:

1. Smithard DG: Dysphagia: A Geriatric Giant? Med Clin Rev 2016; 02.
2. Bahareh-Bakhshaie P: Dysphagia - Pathophysiology of swallowing dysfunction, symptoms, diagnosis and treatment. J Otolaryngol Rhinol 2019; 5(3). doi:10.23937/2572-4193.1510063
3. Kakar S, Singh R and Kumar S: Orodispersible tablets: an overview. MOJ Proteomics Bioinforma 2018; 7(3): 180-82.
4. FDA: Guidance for Industry: Orally Disintegrating Tablets 2008.
5. Rada S and Kumari A: Fast dissolving tablets: waterless patient compliance dosage forms. J Drug Deliv Ther 2019; 9: 303-17.
6. Zhang Y shuai, Li J dong and Yan C: An update on vinpocetine: New discoveries and clinical implications. Eur J Pharmacol 2018; 819: 30-34.
7. Al-Kuraishy HM, Al-Gareeb AI, Naji MT and Al-Mamorry F: Role of vinpocetine in ischemic stroke and poststroke outcomes: A critical review. Brain Circ 2020; 6(1): 1-10.
8. Alyami H, Dahmash E, Bowen J and Mohammed AR: An investigation into the effects of excipient particle size, blending techniques and processing parameters on the homogeneity and content uniformity of a blend containing low-dose model drug. PLoS One 2017; 12(6). doi:10.1371/journal.pone.0178772
9. Moqbel HA, ElMeshad AN, El-Nabarawi MA.: A pharmaceutical study on chlorzoxazone orodispersible tablets: formulation, *in-vitro* and *in-vivo* evaluation. Drug Deliv 2016; 23(8): 2998-3007.
10. British Pharmacopoeia; 2017.
11. Shah J, Tomar M, Singh AK and Sinha AR: Study of microcrystalline cellulose as a substitute of magnesium stearate towards functionality of lubricant in aspirin formulation. Int J Dev Res 2017; 7(10): 15879-84.
12. Abbas A, Ibrahim W, Sakran W and Badawi A: Evaluation and characterization of sildenafil 50 mg orodispersible tablets using sublimation technique. J Adv Pharm Res 2018; 2(4): 292-311.
13. Chauhan D, Sagar MK and Kumar S: Formulation and in-vitro evaluation of oro-dispersible tablet of dabigatran. Int J Adv Sci Technol 2019; 28(15): 569-78.
14. Preethi S and Jain V: Formulation and evaluation of an emtricitabine adjustable pediatric anti-retroviral dosage form. Drug Invent Today 2019; 12(1): 76-83.
15. Bhat P, Mulgund S and Vora S: Development and validation of a UV spectrophotometric method for estimation of vinpocetine in bulk and tablet dosage form. Asian J Pharm Res Dev 2013; 1: 83-87.
16. Mobarak DH, Salah S and Ghorab MM: Formulation and evaluation of oro-dispersible tablets of tadalafil self emulsifying drug delivery system. Inventi Impact Pharm Tech 2015; 3: 145-55.
17. Kharshoum RM, Sanad RA and Ali AMA: Comparative pharmacokinetic study of two lyophilized orally disintegrating tablets formulations of vinpocetine in human volunteers. Int J Drug Deliv 2013; 5(2): 167-76.
18. Jadhav RT, Patil PH and Patil PR: Formulation and evaluation of bilayered tablet of piracetam and vinpocetine. J Chem Pharm Res 2011; 3(3): 423-31.
19. Iancu V, Roncea F and Cazacincu RG: Response surface methodology for optimization of diclofenac sodium oro-dispersible tablets (ODTs). Farmacia 2016; 64(2): 210-16.
20. Bhargav E, Reddy CSP, Sowmya CH, Khan KAA, Rajesh K and Srinath B: Formulation and optimization of piroxicam orodispersible tablets by central composite design. J Young Pharm 2017; 9(2): 187-91.
21. Kumar MA, Murthy PN, Sameeraja NH and Narayan PN: Dissolution rate enhancement of entacapone and formulation of its oro-dispersible tablets: Applying statistical design. Ind J Phar Edu Res 2016; 50(4): 549-62.
22. Ali BE, Al-Shedfat RI, Fayed MH and Alanazi FK: New methodology for development of orodispersible tablets using high-shear granulation process. Acta Pol Pharm - Drug Res 2017; 74(3): 969-81.
23. El-Dahmy RM, Elsayed I, Elshafeey AH, Gawad NAA El and El-Gazayerly ON: Optimization of long circulating mixed polymeric micelles containing vinpocetine using simple lattice mixture design, *in-vitro* and *in-vivo* characterization. Int J Pharm 2014; 477(1): 39-46.
24. Sharma P and Tailang M: *In-vivo* study of orodispersible tablet of primaquine. IJPSR 2018; 9(8): 3506-10.
25. Comoglu T, Inal O, Kargili A and Pehlivanoglu B: Formulation, *in-vitro* and *in-vivo* evaluation of taste masked rasagiline orally fast disintegrating tablets (ODTS). Res Rev Pharm Pharm Sci 2017; 6(2): 27-38.
26. Moqbel HAM: Pharmaceutical Study on certain fast dissolving dosage forms. MSc Thesis, Faculty of Pharmacy, Cairo University, Egypt 2016.
27. Parasuraman S, Raveendran R and Kesavan R: Blood sample collection in small laboratory animals. J Pharmacol Pharmacother 2010; 1(2): 87-93.
28. Lumsden J, Presidente PJA and Quinn P: Modification of the orbital sinus bleeding technic for rabbits. Lab Anim Sci 1974; 24(2): 345-48.
29. Mcguill WM and Rowan A: Biological effects of blood loss: Implications for sampling volumes and techniques. Ilar News. 1989; 31(4): 5-20.
30. El-Dahmy RMI: Bioavailability enhancement for a central nervous system acting drug. MSc Thesis, Faculty of Pharmacy, Cairo University, Egypt 2016.
31. Wang M, Wang L, Sun J, Zhang L, Zhao L and Xiong Z: Simultaneous determination of vinpocetine and its major active metabolite apovincaminic acid in rats by UPLC-MS/MS and its Application to the brain tissue distribution study. J Chromatogr Sci 2018; 56(3): 225-32.
32. Xia HM, Su LN and Guo JW: Determination of vinpocetine and its primary metabolite, apovincaminic acid, in rat plasma by liquid chromatography–tandem mass spectrometry. J Chromatogr B. 2010; 878(22): 1959-66.
33. Yong Z, Huo M, Zhou J and Xie S: PK Solver: An add-in program for pharmacokinetic and pharmacodynamic data analysis in Microsoft Excel 2010; 99. doi:10.1016/j.cmpb.2010.01.007

34. Canbay HS and Doğantürk M: Application of differential scanning calorimetry and fourier transform infrared spectroscopy to the study of metoprolol-excipient and lisinopril-excipient compatibility. Eurasian J Anal Chem 2018; 13(5): 0-6.
35. Rojek B and Wesolowski M: DSC supported by factor analysis as a reliable tool for compatibility study in pharmaceutical mixtures. J Therm Anal Calorim 2019. doi:10.1007/s10973-019-08223-7
36. Solaiman A, Suliman AS, Shinde S, Naz S and Elkordy A: Application of general multilevel factorial design with formulation of fast disintegrating tablets containing croscaremellose sodium and Disintequick MCC-25. Int J Pharm. 2016; 501. doi:10.1016/j.ijpharm.2016.01.065
37. Rezazadeh M, Mohammadi T, Shahtalebi M, Tavakoli N and Mostafavi SA: Development and evaluation of orally disintegrating tablets of pramipexole using full factorial design. Iran J Pharm Sci 2018; 14(4): 79-90.
38. Sumaiyah S, Mentari J and Suryanto S: The effect of crospovidone on the dissolution profile of amlodipine besylate from fast orally dissolving film. Open Access Maced J Med Sci 2019; 7(22): 3811-15.
39. Kumar RS and Kumari A: Superdisintegrant: crucial elements for mouth dissolving tablets. J Drug Deliv Ther 2019; 9(2): 461-68.
40. Mushtaq M, Fazal N and Niaz A: Formulation and evaluation of fast-disintegrating tablets of flurbiprofen and metoclopramide. J Pharm Innov 2020. doi:10.1007/s12247-020-09455-z
41. The United States Pharmacopeia (USP 40); 2017.
42. Remington: The Science and Practice of Pharmacy. 22nd edition 2013.
43. Radicioni M, Castiglioni C, Giori A, Cupone I, Frangione V and Rovati S: Bioequivalence study of a new sildenafil 100 mg orodispersible film compared to the conventional film-coated 100 mg tablet administered to healthy male volunteers. Drug Des Devel Ther 2017; 11: 1183-92.
44. Masih A, Kumar A, Singh S and Tiwari AK: Fast dissolving tablets: A review. Int J Curr Pharm Res 2017; 9. doi:10.22159/ijcpr.2017v9i2.17382

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