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Implementing novel expert systems in the design of personalized paediatric pyridoxine hydrochloride orodispersible tablets

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ABSTRACT: This research implements a computer-aided formulation development algorithm based on a novel SeDeM-ODT expert system in establishing the design space for paediatric pyridoxine hydrochloride orodispersible tablets (ODTs) using Prosolv® ODTG2, Prosolv® EasyTab SP, and Ludiflash® systems. For each formulation ingredient, expert system-defined preformulation parameter values were experimentally determined according to standardized methods and then normalized to the theoretical radius range [0,10]. Expert diagrams were constructed and the quantitative performance of each ingredient was evaluated using parametric profile index (IPP), flowability (ff'), and compressibility (ff_c) functions. The net direct compression capability was quantitatively expressed as the product of expert system reliability and IPP. Direct compression was conducted in an eccentric tablet press and properties were evaluated using weight, dimension, disintegration test, contact angle, tensile strength, x-ray diffraction, and Fourier-transform infrared spectroscopy. The ODTs dissolution profiles were fitted and compared using zero-order, first-order, Hixson-Crowell, and Hopfenberg models. Results of the expert diagram of pyridoxine hydrochloride indicated suboptimal normalized radii values in 8 out of 12 parameters, implying a compromised mechanical zone (ff'=3.61, ff_c=2.11). By setting a target ff_c for the optimized formulation mix at 5.0, the predicted proportions of the fillers to remedy the direct compression deficits of the drug were computed as 89.00%, 83.23%, and 76.62% for Prosolv® ODTG2 (ff_c=5.36), Prosolv® EasyTab SP (ff_c=5.58), and Ludiflash® (ff_c=5.88), respectively. The produced ODTs were of acceptable target quality, hence the SeDeM-ODT system was considered a reliable formulation tool for establishing the design space of this particular drug-filler systems.

KEYWORDS: paediatric-centric formulations; orodispersible systems; computer-aided drug design; expert systems; pyridoxine hydrochloride; direct compaction technology

1. INTRODUCTION

The impact of evolving regulations has necessitated special paediatric investigative plans in the formulation development of dosage forms for paediatrics [1,2]. This is necessary because the paediatric population is heterogenous with extensive variation in physiology, anatomy, and cognitive development [3]. Although in this population, the liquid dosage forms present the most suitable oral delivery system,

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numerous critical patient, formulation, and manufacturing considerations such as stability, cost, posology, taste-masking, and acceptability, have justified the exploration of monolithic solid dosage forms [4,5]. Administration of conventional monolithic tablets or capsules is however impractical in paediatric patients younger than 6 years as it is associated with high risks of asphyxiation, particularly in infants and toddlers, in whom buccal manipulation and swallowing of tablets may not be properly coordinated [6]. Similarly, patients with dysphagia, oropharyngeal carcinoma, stroke, or Parkinson's disease typically present with impaired muscle tone and uncoordinated peristaltic waves to propel ingested tablets down the oesophagus [6]. Under the current European legislative frameworks, paediatric drug development must be tailored to meet the unique requirement of this population [1,2].

Orodispersible tablets (ODTs) are innovative oral drug delivery alternatives to conventional monolithic tablets that rapidly disintegrate in the oral cavity to ease swallowing, without prior mastication or supplementary water intake [4,7]. Numerous clinical studies have pointed to increased patient acceptability of the ODTs formulations [5]. Novel patented and generic technologies based on lyophilization [8,9], 3-D printing [10,11], moulding [12,13], and cotton candy [4,14] are available options for ODTs manufacturing. However, the cost implications, limited therapeutic scope, scale-up, long-term stability, dosage precision, and product fragility issues are serious concerns that impact sustainable large-scale commercial manufacturing, and also on routine clinical applications. Consequently, direct compression tablet manufacturing technology has been adapted as a cost-effective alternative for sustainable production of ODTs [15–17]. The technology utilizes fewer unit operations, equipment, and validation procedures compared to roller compaction or wet granulation technologies for manufacturing tablets [18–20]. However, this apparent simplicity holds only when the formulation ingredients satisfy the stringent multifunctional technical requirements of efficient flow, compaction, and disintegration [21]. In practice, only very few pharmaceutical solid materials are true candidates for direct compression [21,22].

Another compelling challenge in the formulation design of orodispersible systems via the direct compression route is the complexity in the selection of an appropriate design space [23]. The critical material attributes, process parameters, and the output target quality product profile relate in a non-linear and complex pattern [24]. Hence, the determination of optimized formulation parameters that would give ODTs of acceptable target quality profiles requires numerous repeated empirical trials or design of experiments, which are non-economical and time-consuming [25]. Computer-aided formulation design tools have evolved to resolve complex pharmaceutical formulation problems and reduce the time to market developed products [26,27]. The SeDeM expert system is an emerging computer-aided formulation development algorithm for the rational design of tablets via direct compression. The generated expert data informs formulation scientists and engineers of the degree to which powder formulation ingredients could produce ODTs of acceptable target quality without trial-and-error and minimal experimental runs [28,29]. The novel SeDeM-ODT expert system specifically focused on formulation design and optimization of ODTs via DC technology [16,30,31]. The novel algorithm simultaneously characterizes rheological behaviour, compressibility, dosage uniformity, stability, and orodispersibility/bucodispersibility of the powder formulation ingredients and quantitatively predicts the optimized numerical solution to compensate for compression deficits [30–32]. In addition to serving as a quality control tool for monitoring batch-to-batch reproducibility, the tool has been used to compare the direct compression performance of fillers from the same or different chemical families [33]. The expert tools have been successfully applied in the adult formulation of tablets for oral delivery of carbamazepine [34], captopril [35], ibuprofen [36], zidovudine[37], and rosuvastatin [15]. However, few studies utilized the tools in the formulation design of paediatric ODTs [38].

It is crystal clear that current European legislative frameworks on paediatric investigative plans strengthen reciprocal attention to paediatric-focused development [1,2]. Therefore, the goal of this study was to implement SeDeM-ODT expert system in the systematic design of paediatric-focused pyridoxine hydrochloride ODTs using commercially established brands of orodispersible coprocessed fillers based on Prosolv® ODTG2, Prosolv® EasyTab SP, and Ludiflash®. These coprocessed fillers are multifunctional coprocessed products designed specifically for ODTs manufacturing via direct compression. Pyridoxine hydrochloride is indicated for the management of isoniazid (INH)-induced peripheral neuropathy, INH and monomethylhydrazine poisoning, as well as vitamin B6 replenishment in deficiency states [39,40]. Thus, this study critically implements the SeDeM-ODT expert system in the design space of paediatric-centric pyridoxine hydrochloride ODTs the Prosolv®ODTG2, Prosolv® ODTG2, and Ludiflash® powder systems.

2. RESULTS AND DISCUSSION

2.1 SeDeM diagram and preformulation properties of pyridoxine HCl

The goal of the SeDeM expert algorithm in preformulation studies is to quantitate, validate, and predict the direct compression appropriateness of powder formulation ingredients so that corrective plans can be precisely and proactively implemented [25,41]. The SeDeM expert diagram could be regarded as a 'diagnostic' tool that is applied to graphically summarize the aptness of a formulation ingredient in a powder state to be processable via direct compaction method [25,42]. A typical SeDeM expert diagram is an *n*-sided regular polygon, where *n* represents the number of experimentally determined preformulation parameters. For any given *n*-sides, there are also *n*-radii each interconnecting the centre of the polygon to the vertices [24,25]. Each radius, *r* serves as a linear scale for measuring the magnitude of a particular parameter. When experimentally determined values are normalized into a linear scale between 0 to 10, and then constructed as a SeDeM diagram, a characteristic shape whose size represents the extent of the parameter is formed. There are three important regions in the diagram; the centre (r=0), the mid region (r=5.0), and the vertices (r=10.0). The desirable limit for each parameter is $10 \geq r \geq 5.0$. All shaded regions at r<5.0 implied technical deficiency [24,25].

For pyridoxine hydrochloride only 4 out of 12 parameters had limits within the theoretically acceptable limit (Figure 1). Similarly, from other SeDeM expert functions presented in Table 1, the parametric profile index (IPP) of the drug was below the acceptable limit of 5.0. For flowability (ff′), the drug demonstrated substantial limitations (ff′ = 3.61). The observed low ff′ function could be ascribed to the zero scores of static angles of repose (AR) and mass powder discharge rate (t″). The predicted implications of this value would be non or poor flow of the drug powder coupled with inconsistent die filling during compression events. The net effect of an inefficient powder flow pattern compromises the critical quality of accurate ODTs weight and dosing.

Compressibility function (ff_c) is another critical material attribute that must be considered before a material is subjected to direct compression. Despite attaining an acceptable compressibility index (IC=5.45), the overall ff_c function was suboptimal to yield a compact of acceptable mechanical profile. This was secondary to lower cohesion index (Icd) and friability (Fr) radii values. This means that the drug particles do not form appreciable intermolecular bonds such as hydrogen bonding, electrostatic attractions, and van der Waals forces to form mechanically stronger compact.

In the SeDeM system, the function lubricity/dosage predicts the homogeneity of the powder system which is defined by particle size <75 µm (%Pf) and homogeneity index (Iθ). The drug was short of this function as it equally failed to satisfy lubricity/stability, a measure of stability to ambient hygroscopicity. The overall direct compression suitability of pyridoxine hydrochloride (IGC=3.83) does not favour direct compression. However, all of these deficiencies could be corrected using multifunctional high functionality direct compression coprocessed excipients used in this study.

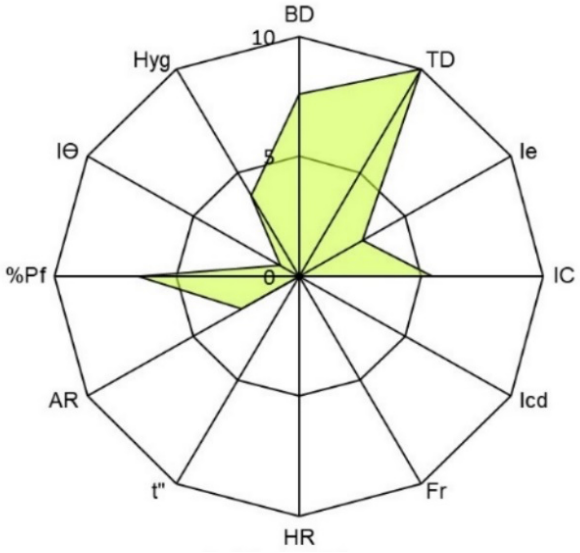

Figure 1. SeDeM expert system diagram of pyridoxine hydrochloride.

Table 1. Incidence functions, parameter profile, parametric profile index, and index of good compression and bucodispersion.

Coprocessed Fillers/Drug	functions					IP[f]	IPP[g]	IGC/IGCB[h]
	D[a]	ff_c[b]	ff'[c]	LD[d]	BD[e]			
Pyridoxine hydrochloride	9.02	2.11*	3.61	3.71	N.A	0.42	4.05	3.83[i]
Prosolv® ODT G2	6.80	5.36	8.20	3.78	8.78	0.71	6.36	6.14
Prosolv® EasyTab SP	4.63	5.58	7.79	2.62	9.39	0.71	5.84	5.64
Ludiflash®	5.13	5.88	7.59	2.33	4.60	0.71	5.44	5.25

[a] Dimension. [b] Compressibility function. [c] Flowability function. [d] Lubricity/dosage. [e] Bucodispersion.
[f] Parameter profile. [g] Parametric profile index. [h] Index of Good Compression/Bucodispersion.
[h] Index of Good Compression value for pyridoxine hydrochloride. N.A.: Not applicable

2.2 SeDeM-ODT diagrams and preformulation characteristics of the coprocessed fillers

The SeDeM-ODT expert diagram is an extended form of the normal SeDeM expert system that includes two additional design parameters; disintegration time with disc (DTD) and disintegration time without disc (DTN), which define bucodispersion function. Therefore, the SeDeM-ODT diagram of each coprocessed filler is a 14-sided regular polygon in contrast to the 12 sides of the pyridoxine hydrochloride. The diagram explicitly revealed the superiority of the coprocessed filler over that of pyridoxine hydrochloride (Figure 2). This superiority is reflected by the expanded shaded portion relative to the unshaded portions. Reference is made to the functions in Table 1 for a comparative analysis of the strengths and limitations of the studied ingredients. Both coprocessed fillers had similar parameter profiles (IP=0.71) indicating acceptable direct compression and bucodispersion propensities. In other words, 71% of the radii had acceptable values≥5.0. The ff' and ff_c functions were acceptable. Cumulatively, the attainment of theoretical limits for IP, IPP, and IGCB by the fillers point to their potential to correct the deficiencies of pyridoxine hydrochloride, while simultaneously offering the required orodispersion property.

As coprocessed excipients, the fillers present enhanced multifunctional performance to solve poor formulation properties of actives.

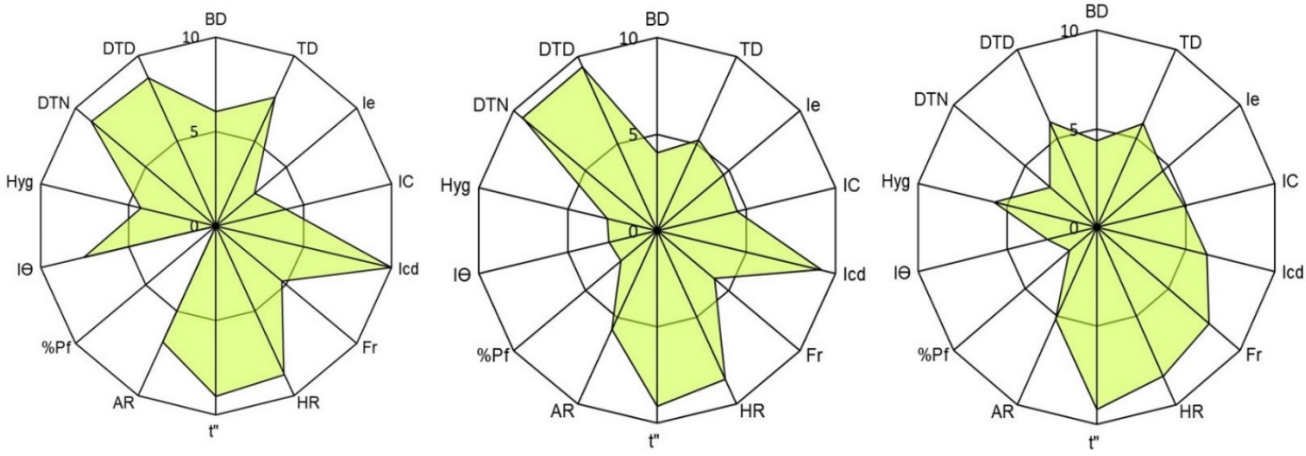

Figure 2. SeDeM-ODT expert system diagrams of coprocessed fillers [Prosolv® ODT G2 (left)], [Prosolv® ODT EasyTab SP(middle)], and [Ludiflash® (right)].

Table 2. Compressibility function optimization procedure for the defective pyridoxine hydrochloride.

Coprocessed fillers/API	Compressibility function of fillers (ff_c)	Target compressibility function of formulation mix (ff_{ct})	Compressibility function of pyridoxine hydrochloride (ff_{cd})	CP[a] (%)
Prosolv® ODT G2	5.36	5	2.11	89.00
Prosolv® EasyTab SP	5.58	5	2.11	83.23
Ludiflash®	5.88	5	2.11	76.62

[a]Proportion of coprocessed filler to correct compressibility function of pyridoxine hydrochloride.

2.3 Optimization of compressibility function

The gross mechanical deficiency of pyridoxine hydrochloride as predicted by the compressibility function (ff_d) points to the need for fillers with superior compression performance to obtain a blend of powder suitable for compression in the tablet press. Despite their divergent, but apt mechanical profile, the coprocessed fillers displayed appreciable propensities to compensate for the compressibility profile of the drug. Based on Equation 3, the predicted proportions of the fillers ranged between 76.62 to 89%w/w to remedy the compressional deficit of the drug whose compressibility function was only 2.11 (Table 2). This indicates that ff_d was critically low for the API and therefore a higher amount of filler was required to raise the incidence of the final formulation to a target value of 5.0. As a computer-aided formulation optimization tool, the ultimate role of the expert systems was to predict the optimum preformulation parameters for the successful tableting process that would result in ODTs with acceptable Target Quality Product Profiles (TQPPs) without empirical trial-and-error. The SeDeM expert diagram profile of the drug predicted in the current work correlates well with previous findings. Scholtz et al have found extremely low angle of repose and powder flow coupled with suboptimal flowability and compressibility indices which agrees with our reported values [43]. This supported the high proportions of the coprocessed fillers utilized in the optimization procedure as predicted by Equation 3. The success of the ODTs production process was also partly ascribed to the high proportion of the corrective excipients above the drug, which constituted only 10 mg of the target weight. Based on established principles of percolation theory [44–46], we could hypothesize that the coprocessed fillers dominated the entire powder system. Coprocessed products have been demonstrated to offer synergistic flowability, compressibility, compactability, and tabletability in tablet formulation process [18,47–49], and this has contributed to the formation of acceptable ODTs.

2.4 Properties of the formulated orodispersible tablets

2.4.1 ODTs weight and dimension

Although ODTs are designed to disintegrate in the buccal cavity, the final weight and dimension of an ODT need to be factored in the design of paediatric dosage form to enable handling and buccal manipulation. The Food and Drug Administration Guidance for Industry, recommends ODT weight of <500 mg. In this study, the mean ODTs weight and dimension were shown in the control chart (Figure 3) and Table 3, respectively. Clinical studies have found such tablet dimensions acceptable among paediatric population [50]. It is worth noting, the variation of the mean tablet weight from upper and lower control limits.

Considering the SeDeM-ODT diagrams of the fillers, the parameter radii values of AR, t", HR, which cumulatively defined the flowability functions were within the acceptable limit (r≥5.0) (Figure 2). Having satisfied this direct compression requirement, reproducible metering of formulation mix into die cavities was achieved during compression cycles, hence consistent ODTs weight. It is also of interest to note the SeDeM expert diagram of pyridoxine hydrochloride. Although flowability parameters were below the minimal acceptable threshold, the existence of a high proportion of the fillers predominated the entire formulation mix, thereby resolving the flow compromises due to pyridoxine hydrochloride.

2.4.2 Mechanical properties

ODTs produced by direct compression should be mechanically strong to withstand subsequent manufacturing operations such as coating, polishing, and packaging, as well as during transportation and patient use. The SeDeM-ODT predicted compressibility function was measured by cohesion index (Icd), Fr,

and IC radii values. The latter predicts volume reduction propensity, while Icd measures compactability. Fr was included as part of the function to account for the mechanical stability of the formed ODTs.

Table 3. Dimension, mechanical, and disintegration properties of the orodispersible formulations.

Orodispersible formulation	ODT dimension			Tensile strength (MNm^{-2})	Friability (%)	Disintegration time (seconds)	Contact angle (°)
	l[a](mm)	T[b](mm)	w[c] (mm)				
F1	9.86[d] ± 0.03[e]	3.91 ± 0.03	2.93 ± 0.04	1.68 ± 0.17	0.57	17.5 ± 4.6	18
F2	9.89 ± 0.03	3.93 ± 0.03	2.91 ±0.11	1.79 ± 0.13	0.46	10.8 ± 1.1	23
F3	9.91 ± 0.02	3.97 ±0.01	3.76 ± 0.11	1.86 ± 0.18	0.61	34.5 ± 4.5	29

[a] Length of the long tablet axis, [b]Tablet thickness, [c] Central cylinder thickness
[d] Mean, [e]Standard deviation

During the preformulation phase, all the fillers exhibited acceptable radii values of IC and Icd (Figure 2). Fr was attained only by Ludiflash®. However, the cumulative ff_c was attained by all three excipients because their Icd radius value was very high. To resolve the Fr compromises, the compaction load was adjusted in the final formulation, which resulted in mechanical properties indicated in Table 3.

2.4.3 Disintegration time

Orodispersion is the most contrasting feature between conventional monolithic dosage forms and ODTs, in addition to taste-masking properties. ODTs are designed to rapidly disintegrate in the oral cavity without chewing or water intake [7]. In this research, we defined bucodispersion as *in vitro* disintegration with an upper limit of 180 seconds (3 min) in the presence (DTD) or absence of disc (DTN). The rapid disintegration of all three ODTs could be attributed to the presence of superdisintegrant in the coprocessed matrix resulting in strong absorption of water molecules and rapid bursting of the tablet structure. Studies on contact angles have further supported these findings (Table 3). The low contact angle of water droplets on the surface of the ODTs signifies a high propensity of contact and hence higher chances of wetting and subsequent disintegration [51].

2.4.4 Drug-excipients compatibility

The FTIR spectra of pyridoxine hydrochloride comprise distinct vibrational modes characteristic of the pyridine ring, CH_3, CH_2, CH, and OH groups (Figure 4). Vibrational modes at 3652, 3324, and 3231cm^{-1} were characteristic of O-H stretching. Angle bending associated with C-OH occurred at 1150-1450 cm^{-1}. C-H out-of-plane bending and C-H stretching in CH_3 functional groups were observed at 3000-3100 and 1350-950 cm^{-1}, respectively. Stretching modes due to the CH_2 attached to the side chains were observed at 3086 cm^{-1}. Twisting and wagging modes associated with CH_2 were observed at the regions 1200-1185 and 1407-1395 cm^{-1}. The CH_2 group-induced scissoring occurred at 1512 cm^{-1}. The pyridine ring-associated stretching vibrations manifested at 1483, 1543, 1330, 1274, and 1215 cm^{-1} [52]. The FTIR spectra of the various ODTs formulations preserved similar vibrational modes, however with additional absorption characteristics of functional groups due to the primary excipients constituting the coprocessed structure. Similarly, the XRD patterns due to the crystalline peaks of the pure pyridoxine were also maintained in the orodiperisble formulations which are suggestive of the absence of phase transition (Figure 5).

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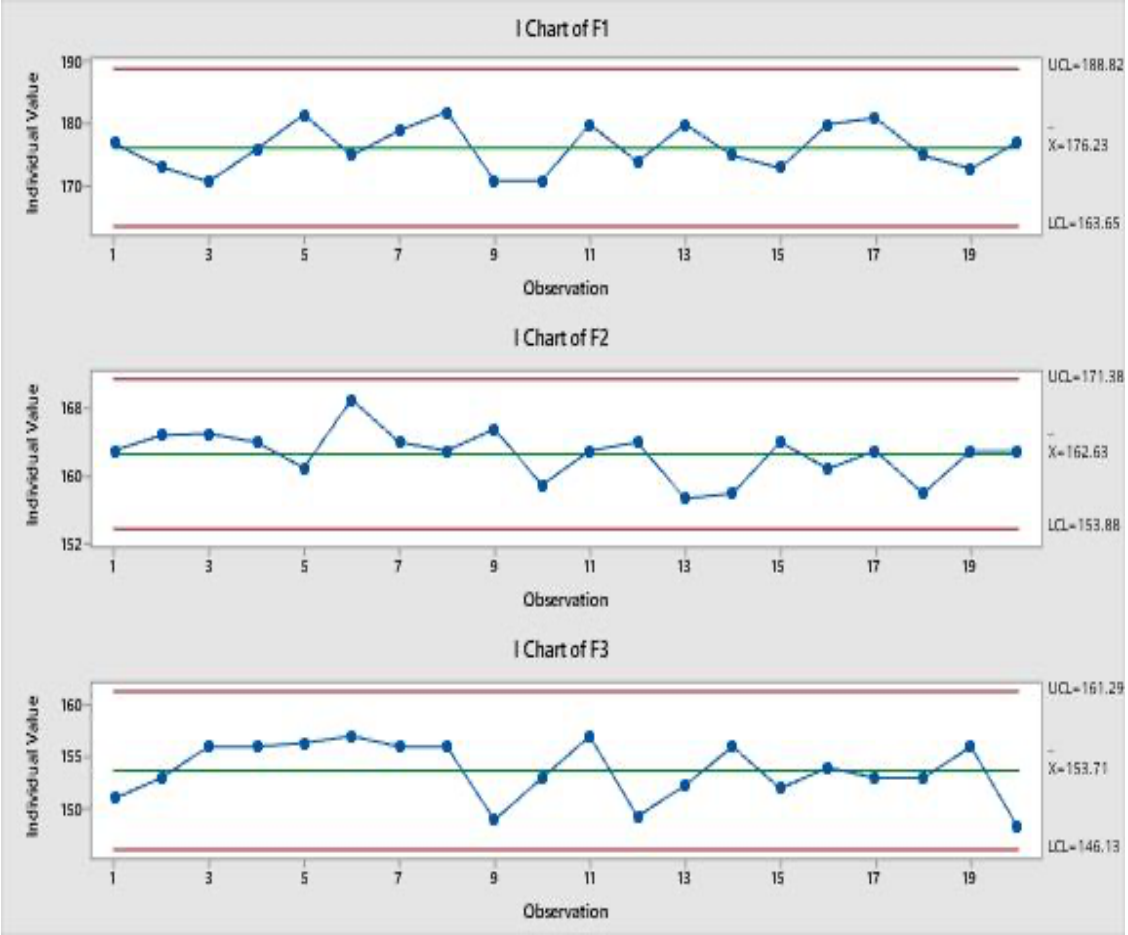

Figure 3. Weight variation of the formulated orodispersible formulations.

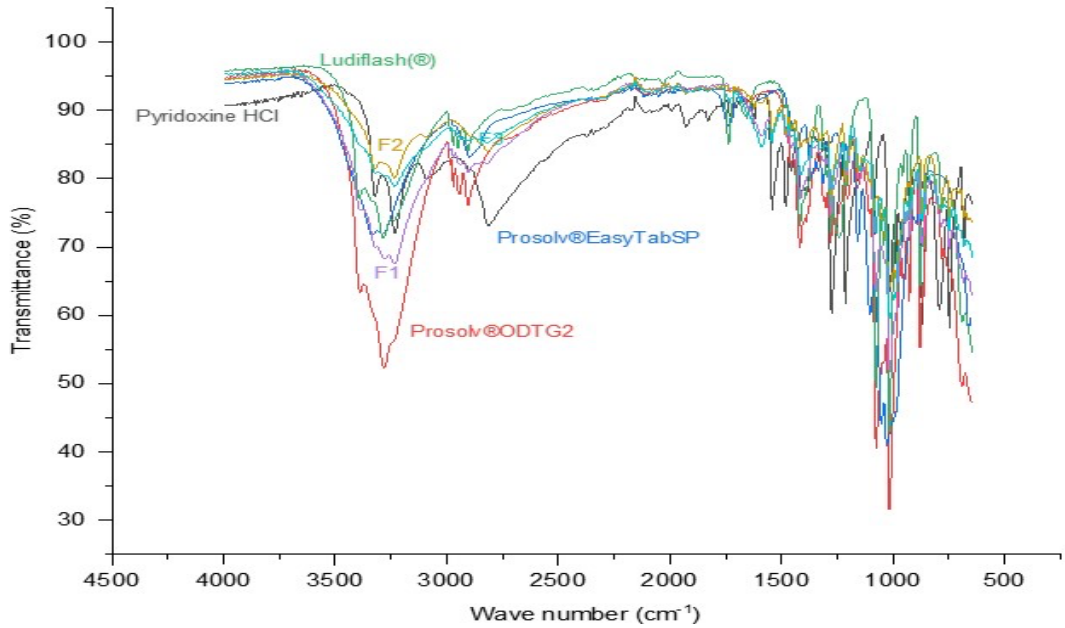

Figure 4. Fourier-transform infrared spectra of orodispersible formulations.

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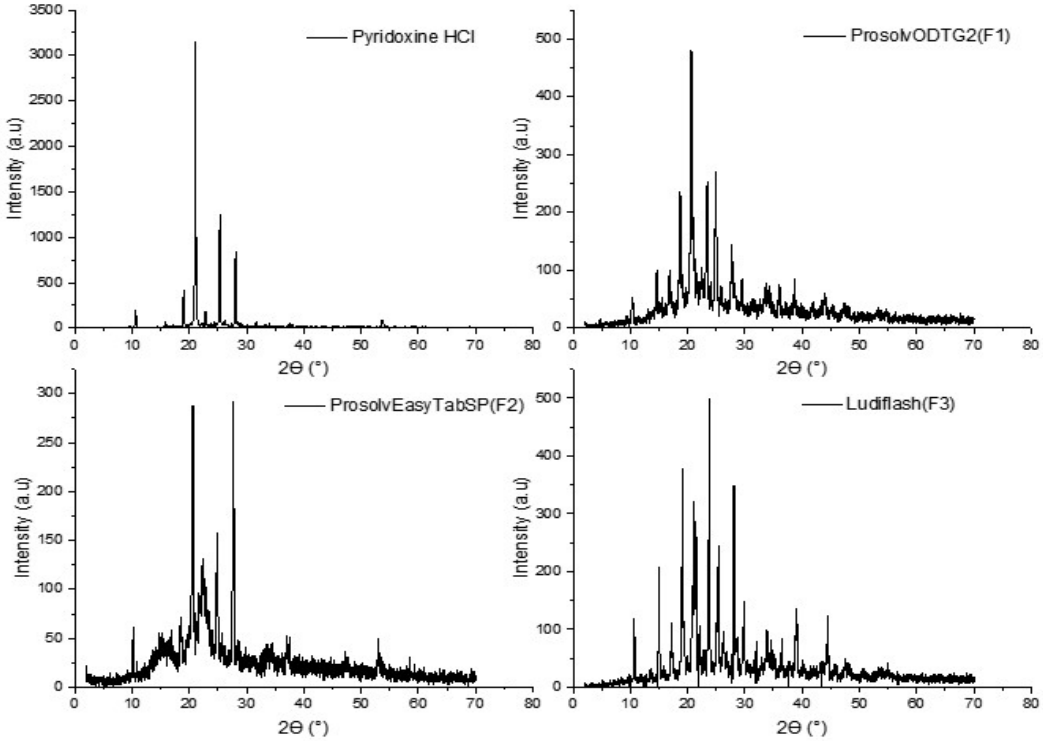

Figure 5. X-ray diffraction patterns of the drug and orodispersible formulations.

2.4.5 Drug content and release kinetics

The drug content and dissolution profiles are important critical quality attributes of formulated ODTs. In all the formulations, the pyridoxine hydrochloride content was United States Pharmacopoeia [53]. As an immediate-release dosage form, >80% of the drug was released in 45 min following dissolution in all the formulations (Figure 6). However, the ODTs displayed diverse drug release kinetics as displayed by the coefficient of determination (R^2), Akaike Information Criterion (AIK), and Model Selection Criterion (MSC). The data fitting indicates that the release kinetics were closer to first-order, Hixson-Crowell, and Hopfenberg models, and also farthest away from zero-order kinetics (Table 4).

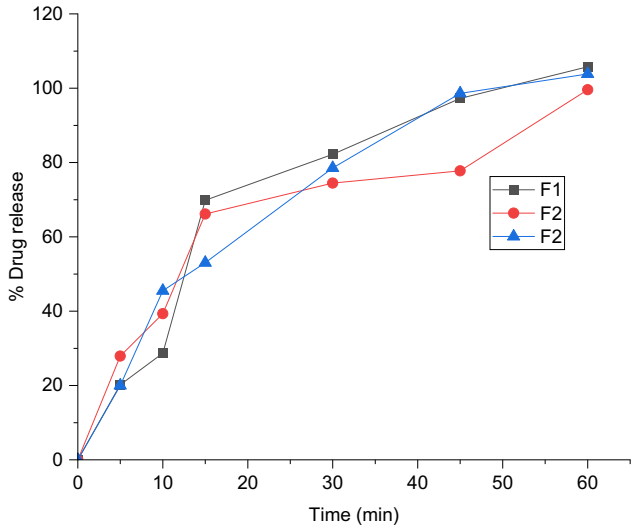

Figure 6. Drug release profiles of the orodispersible formulations. F1: Prosolv® ODTG2, F2: Prosolv®EasyTab SP, F3: Ludiflash®.

Table 4. Drug release kinetics and model evaluation.

Model	Model parameters	Orodispersible formulations		
		F1	F2	F3
Zero-order	k_0[a]	2.13	1.92	2.09
	R^2[b]	0.619	0.213	0.645
	AIC[c]	48.71	49.49	47.31
	MSC[d]	0.63	-0.09	0.70
First-order	k_1[e]	0.06	0.05	0.06
	Rsqr	0.921	0.896	0.973
	AIC	39.25	37.37	31.92
	MSC	2.21	1.93	3.27
Hixson-Crowell	k_{HC}[f]	0.02	0.01	0.02
	Rsqr	0.939	0.815	0.983
	AIC	37.71	40.79	29.08
	MSC	2.47	1.36	3.74
Hopfenberg	k_{HB}[g]	0.02	0.00	0.01
	Rsqr	0.939	0.896	0.984
	AIC	39.71	39.38	30.83
	MSC	2.13	1.59	3.45

[a] Zero-order release constant. [b] Coefficient of determination. [C] Akaike Information Criterion.
[d] Model Selection Criteria. [e] First-order release constant. [f] Hixson-Crowell release constant. [g] Hopfenberg release constant.

3. CONCLUSION

This research demonstrates the utility of the novel SeDeM-ODT expert system in the design of paediatric-centric pyridoxine hydrochloride ODTs using Prosolv® ODTG2, Prosolv® ODTG2, and Ludiflash® powder systems via direct compression technology. Given the low flowability and compressibility functions of the drug, the predicted SeDeM-ODT preformulation parameters of the three fillers demonstrated suitable corrective propensities to compensate for the mechanical deficiencies of the drug at higher proportions (76.62 to 89.00). Based on established principles of percolation theory, we hypothesized that the domination of the coprocessed fillers over pyridoxine hydrochloride in the optimized formulation blends had resulted in ODTs with an acceptable target quality product profile. Based on the weight control charts together with the wetting, mechanical, and drug release properties, it could be inferred that the optimized formulation procedure predicted by the SeDeM-ODT expert system has resulted in powder formulation ingredients with desired critical material attributes to yield stable conditions for orodispersible tablet manufacturing of pyridoxine hydrochloride.

4. MATERIALS AND METHODS

4.1 Materials

The model active pharmaceutical ingredient pyridoxine hydrochloride was received as a donation from Vitro Health Nigeria LTD. The details of experimental directly compressible coprocessed fillers are presented in Table 5.

Table 5. Details of the experimental directly compressible coprocessed fillers.

Coprocessed coprocessed fillers	Ingredients/Composition	Manufacturer
Prosolv® ODT G2 Lot No.: Q2D6L18	Mannitol, Microcrystalline Cellulose, Crospovidone, Anhydrous Silicic Acid, Colloidal Silicone Dioxide, Silica, Colloidal Anhydrous	JRS Pharma, GMBH & CO. KG, Rosenberg, Germany
Prosolv® EasyTab SP Lot No.: 6809070808	Microcrystalline Cellulose, Colloidal Anhydrous, Silica, Colloidal Anhydrous, Sodium stearyl Fumarate, Sodium starch glycolate.	JRS Pharma, GMBH & CO. KG, Rosenberg, Germany
Ludiflash® Lot No.: 91941247G0	D-Mannitol, Kollidon® CL-SF, Polyvinyl acetate, and Povidone.	BASF, Ludwigshafen, Germany

[a] United States Pharmacopoeia. [b] European Pharmacopoeia.
[c] National Formulary. [d] Japanese Pharmacopoeia.

4.2 Methods

4.2.1 SeDeM and SeDeM-ODT expert systems preformulation analysis of powder ingredients

The preformulation analysis of pyridoxine hydrochloride was conducted using the conventional SeDeM expert system, while for the co-processed fillers, the novel SeDeM-ODT expert system (14 parameters) was adopted. Both expert systems share similar parameters except for bucodispersion which was peculiar to the latter. Pharmacopoeial parameters were experimentally determined as described under relevant sections of the United States Pharmacopoeia (USP41-NF 36) with slight modifications that were necessary. Non-pharmacopoeial parameters were characterized using established methods. Essentially, the parameters were sub-classified into five domains (functions), namely dimension, compressibility, flowability, lubricity/dosage, and lubricity/stability. The SeDeM-ODT system has an additional bucodispersion function. The total number of parameters, acceptable theoretical range, and normalization factors for each ingredient are detailed in Table 6 [24,43]. The methods for the measurement/determination of these parameters have been reported in sufficient detail in relevant literature [16,24,31,54].

Bulk (BD) and tap (TD) densities were determined as the ratio of the powder weight to the bulk and tap volumes, respectively. Hausner's ratio (HR), Carr's index (IC), and Interparticle Porosity (Ie) were derived from the bulk and tap densities using equations stated in Table 6. Powder flow (t") was determined as the time taken for a weighted mass of powder to evacuate from the funnel of the Erweka flow test machine (model GDT, Germany). The angle of repose (AR) was expressed as the angle made by the base of the powder cone to the

horizontal surface. Hygroscopicity (Hyg) was determined as the percentage increase in weight of powders exposed to 75% relative humidity in a desiccator [24,31].

Table 6. Description of the parameters included in the expert systems [16,24,31].

		Parameter name/Symbol	Equations	Theoretical range	Normalization factor for conversion to radius range (0,1)
Functions	Dimension[a]	Bulk density (BD)	$BD = m/V_b$	0-1 g/cm^3	$10p$[b]
		Tapped density (TD)	$TD = m/V_t$	0-1 g/cm^3	$10p$
	Compressibility	Interparticle porosity (Ie)	$Ie = TD - BD/TD \times BD$	0-1.2	$10p/1.2$
		Carr's index (IC)	$IC = 100 \times (TD - BD)/TD$	0-50 %	$p/5$
		Cohesion index (Icd)	Experimental	0-200 N	$p/20$
		Friability(Fr)[c]	$Fr = 100(w_1 - w_2)/w_1$	1-0 %	$10 - 10p$
	Flowability	Hausner's ratio (HR)	$HR = TD/BD$	3-1	$(30 - (10p))/2$
		Powder flow (mass discharge rate) (t")	$t" = m/time$	20-0 sec	$10 - (p/2)$
		Static angle of repose (AR)[d]	$AR = tan^{-1}(h/r)$	50-0 °	$10 - (p/5)$
	Lubricity/Dosage	Particle size <75µm (%Pf)[e]	Experimental	50-0 %	$10 - (p/5)$
		Homogeneity index (Iθ)	Experimental	0-2x10^{-2}	$500p$
	Lubricity/stability	Hygroscopicity (Hyg)	Experimental	20-0 %	$10 - (p/2)$
	Bucodispersibility[f]	Disintegration time (with disc) (DTD)	Experimental	180-0 sec	$10 - (p/18)$
		Disintegration time (without disc) (DTN)	Experimental	180-0 sec	$10 - (p/18)$

a m is the weight of the powder, while V_b and V_t were bulk and tap volumes, respectively
b Experimentally determined parameter value.
c w_1 and w_2 were respectively the initial and final weights of tablets before and after tumbling in the friability machine.
d. h and r represent the height and the radius of the powder cone, respectively.
e The original SeDeM expert system considered Particle size <50 µm.
f These tests do not apply to the active drug.

To determine cohesion index (Icd), 120 ± 3mg compacts were formed in a single punch tablet press (SSP-12, Shakti, India) equipped with 8 x 4 mm elongated convex-faced punch tooling under compression load of 5 kN. The standardized formular of lubricants (0.14% Aerosil®, 1% magnesium stearate, and 2.36% talc) recommended by the expert system were applied for compression of pyridoxine hydrochloride. Thereafter, the force required to diametrically fracture the tablets was recorded as the cohesion index using a tablet hardness tester (THT-2, Biobase, India). Friability was determined as the fractional loss in tablet weight following the tumbling of tablets in the drum compartment of the friability machine (TFT-3 Biobase, India) operated at 25 ± 1 revolutions per minute. Since the tablets were <650 mg in weight, an equivalent of 6.5 g of tablets were used for the friability test [16,24,31,54].

For analysis of the homogeneity index (IΘ), a sample equivalent to 100±1 g was subjected to 10 minutes of mechanical vibration in a nest of sieves and the index was calculated according to Equation 1 [43]. For the percentage of particles less than 75 µm (%Pf), the powder proportion passing through the 75 µm sieve was recorded [24,31].

$$I\Theta = {P_m} \Big/ {100 + (d_m - d_{m-1})F_{m-1} + (d_{m+1} - d_m + \ldots. + (d_m - d_{m-n})F_{m-n} + (d_{m+n} - d_m)F_{m+n}}$$

Equation 1

where:

P_m: The proportion of powder particles that fall inside the dominant range

F_{m-1}: The proportion of powder particles that fall in the range immediately below the dominant range

F_{m+1}: The proportion of powder particles that fall in the range immediately above the dominant range

d_m: Mean diameter of the particles in the dominant range

d_{m-1}: Mean diameter of the particles in the range immediately below the dominant range

d_{m+1}: Mean diameter of the particles in the fraction of the range immediately above the dominant range

n: Order number of the fraction studied under a series, with reference to the dominant proportion

For the disintegration time with disc (DTD) and disintegration time without disc (DTN), the tests were conducted according to the procedure described in monograph 701 of USP41-NF 36 in which 6 tablets were placed in the tubes of the basket assembly of the disintegration apparatus (Type BK-BJ3, Biobase, India). The medium was distilled water maintained at 37 ± 1 °C. The time taken for the orodispersible tablet units to completely disintegrate and leave the mesh of the basket rack assembly was noted.

4.2.2 Normalization of experimental parameters to radius values and construction of SeDeM and SeDeM-ODT expert diagrams

To convert the experimentally determined parameter value (p) into a radius (r) range (0,10), the values were multiplied with normalization factors enlisted in Table 6. The lower and upper limits of bucodispersion were set at 180 to 0 seconds, respectively. The normalized radius values were converted into 12-sided SeDeM and 14-sided SeDeM-ODT diagrams for pyridoxine HCl and the coprocessed fillers, respectively. All computations and construction of diagrams were conducted using Microsoft Excel (2010 version).

4.2.3 Derivation of net compressibility and bucodispersion indices

IGC and IGCB were calculated as the product of reliability and parametric profile index as indicated in Equation 2. The reliability (R) was computed from the ratio of the area of n-sided regular polygon (A_n) to the area of a circle (A_c) (Equation 3). The radius values of the polygons and the circle equals 10 units. The parametric profile index is the mean values of all determined parameter radii values.

$$IGC\ or\ IGCB = R \times IPP$$ Equation 2

$$R = \frac{A_n}{A_c} = \left(\frac{1}{2} r^2 n \sin\left(\frac{360}{n}\right)\right) \Big/ (\pi r^2)$$ Equation 3

Where n is the number of parameters studied. Hence, for the pyridoxine hydrochloride (n = 12), the reliability was calculated as 0.955. Also for the coprocessed fillers (n = 14) the R value was 0.967 [24].

4.2.4 Optimization of compressibility function of pyridoxine hydrochloride

The optimum amounts of coprocessed fillers required to provide the required compressibility function to pyridoxine HCl ODT were computed according to Equation 4 [25]. The SeDeM-ODT expert system predicted proportions of the fillers were presented in Table 2. This formed the basis for the target tablet weight used in the final formulation.

$$CP = 100 - \left[\frac{(ff_c - ff_t)}{(ff_c - ff_d)} \times 100\right]$$ Equation 4

CP: Percentage of coprocessed filler required to compensate for compressibility deficiency of pyridoxine HCl.

ff_c: Incidence value of the coprocessed filler.

ff_t: Target compressibility incidence value≡5.0.

ff_{cd}: Incidence value of pyridoxine hydrochloride.

4.2.5 Production of pyridoxine hydrochloride orodispersible tablets via direct compaction technology

The calculated amounts of ingredients were weighed and transferred into a V-blender and subjected to a 5 min tumbling mixing at a speed of 100 r.p.m. on All Purpose Equipment (AP-01 Plus, Orchid Scientific, India). The mixed ingredients were fed into the hopper of a single-punch tablet press (SSP-12, Shakti Pharmatech, India), and the die cavity was adjusted via the ejection cam to accommodate the target powder weight for a single ODT unit. The ingredients were compressed at ~6KN using 8x4 mm punch tooling. For each turn of coprocessed filler, punch and die surfaces were thoroughly cleaned with magnesium stearate suspension in acetone.

4.2.6 In-process quality control of and physicochemical characterization of formulated orodispersible tablets

The formed ODT tablets were collected at intervals for in-process quality evaluation. ODTs were visually inspected for physical defects (capping, chipping, and/or lamination) by the operator. The weight of twenty randomly sampled ODTs was determined using a digital analytical balance. Tensile strength (σ_t) was determined taking into cognisance the dimension of the elongated biconvex ODTs (Equation 5) [49,55]. Disintegration time was determined as described under the bucodispersion section.

$$\sigma_t = \frac{2}{3}\left[\frac{10F}{\pi D^2\left(2.84\frac{T}{D} - 0.126\frac{T}{W} + 3.15\frac{W}{D} + 0.01\right)}\right]$$ Equation 5

Where, F is the breaking forces measured using THT-2 digital hardness tester, D, T, W, are the length of the short axis, overall thickness, and tablet wall height.

4.2.7 Fourier-transform infrared spectroscopy

The FTIR spectra of the ODTs and the pure drug were conducted using an infrared spectrometer (Agilent Technologies, Cary 630 FTIR, USA) over the range of 4000-400 cm^{-1}.

4.2.8 X-ray diffraction analysis

X-ray diffraction analysis was conducted using Rigaku Miniflex 600 (Rigaku Corporation, Japan) under the radiation of Cu-Kα (λ=0.1541 nm). Data were collected over 2-theta (2θ) range of 10° to 80° with 1 step/sec rate of scanning [56]. The samples of the various ODTs and the pure pyridoxine hydrochloride were subjected to a voltage and current of 40 kV and 40 mA, respectively.

4.2.9 In vitro disintegration test

This test was conducted as described under section 4.2.1.

4.2.10 Contact angle measurement

The wetting properties of the ODTs were measured using contact angle. Low Bond Axisymmetric Drop Shape Analysis (LB-ADSA) was used for contact angle measurement using ImageJ [57]. Initially, a pendant drop of water from the orifice of a 25-mL burette stationed at a distance of ~2.5 mm away from the surface of the orodispersible tablet was video recorded using the camera of a personal computer (Hp COREi7, 7th Generation). A screenshot of the drop as it just comes in contact with the tablet was acquired and exported to ImageJ. The outline of the drop was aligned by controlling the perturbation functions and contact angle obtained from the drop properties (Figure 7). The same procedure was conducted for all orodispersible formulations.

4.2.11 Drug content, in vitro dissolution, and drug release kinetics

Pyridoxine HCl concentrations in the range of 1.0 to 6.0 µg/ml were spectroscopically measured at λ_{max}= 291 nm, and the absorbances were used to generate a calibration curve and regression equation. For drug content analysis ten tablets from each batch were pulverized using mortar and pestle, and an equivalent of 10 mg pyridoxine hydrochloride was dissolved in 100 mL of 0.1 N HCl following which absorbance was measured. For the dissolution test, an orodispersible tablet from each batch was placed in the basket and lowered into 900 ml of 0.1 N HCl dissolution medium operated at 50 rpm and working temperature of 37 ±2 °C in the dissolution tester (Type BK-RC6, Biobase, India). Aliquots equivalent to 5 mL were withdrawn at intervals and replaced with an equal volume of dissolution medium. The percentage released was quantified with reference to the established regression parameters. Analysis of dissolution data and model evaluation data were conducted using DDSolver. The dissolution data was first fitted with zero-order, first-order, Hixson-Crowell, and Hopfenberg models as described using Equations 6, 7, 8, and 9, respectively. The goodness of fit of the models was evaluated using the coefficient of determination (R^2), Akaike Information Criteria (AIC), and Model Selection Criterion (MSC) [58].

$$F = k_0 t \qquad \text{Equation 6}$$

$$F = (1 - e^{-k_1 t})100 \quad \text{Equation 7}$$

$$F = 100 \times [1 - (1 - k_{HC} t)^3] \quad \text{Equation 8}$$

$$F = 100 \times [1 - (1 - k_{HB} t)^n] \quad \text{Equation 9}$$

Where, F is the percentage drug released at time t, while k_0, k_1, k_{HC} , and k_{HB} are zero-order, first-order, Hixson-Crowell, and Hopfenberg release constants, respectively.

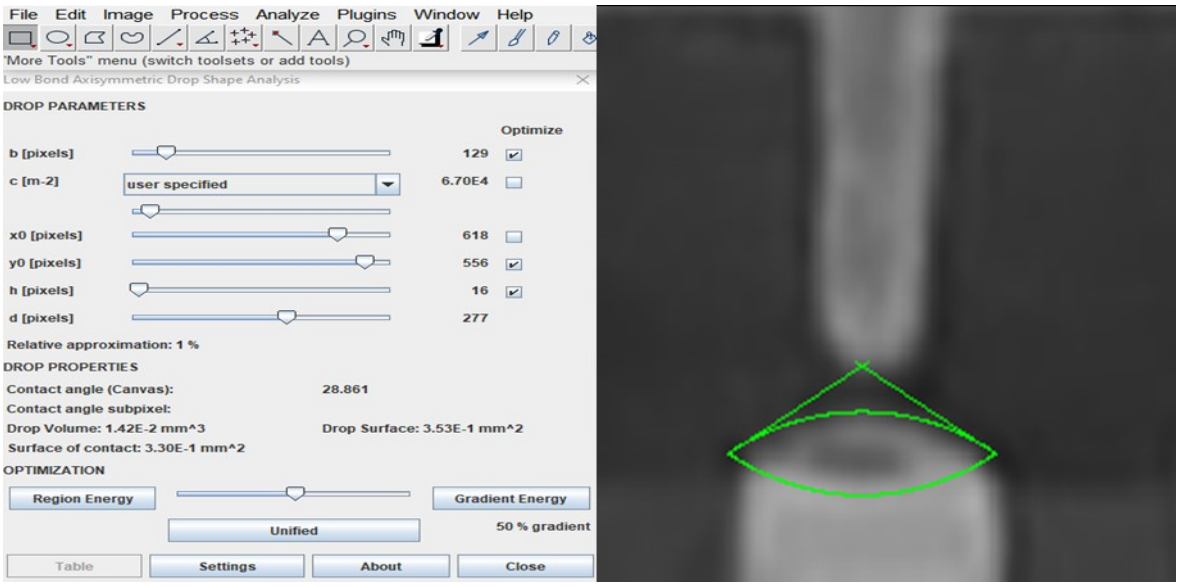

Figure 7. Experimental setup for contact angle measurement. Low Bond Axisymmetric Drop Shape Analysis window in ImageJ (Left). The 8-bt image of the pendant drop (emerging from the burette orifice) as it just wets the surface of the tablet (Right).

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