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Research Article

Development Pharmaceutics of Doxepin Hydrochloride Orally Disintegrating Tablets for Dosing Flexibility to Physicians and Patient Compliance

Packiaraj Jeyachandran Manohari*[1], Venkateswaran Chidambaram Seshadri[1], Madhavan Kumar[1], Kamalakkannan Venkatachalam[2], Jegatheesh Uthayasuriyan[1], Narendra Reddy Parvatha Janarthana Reddy[1], Induprasad Munirathnam[1], Guhan Himadeep Chowdary Eswara Rao[1], Srihariteja Seelamantula[1], Asaithambi Ramesh[1], Samuel Ezhumalai[1], Janakiraman Kunchithapatham[3], Samuel George[4], Aswin Iyappan Seethalakshmi[1], Rohith Sekar[1]

[1] Vice President – Research & Development and Business Development, Hibrow Healthcare Pvt Ltd and Nutrimed Lifesciences Private Limited, Survey No 258, Thiruvandavar Village Sirupinayur Panchayat, Uthiramerur Taluk, Chennai, Tamil Nadu – 603308, India.

[2] Faculty of Pharmacy, SSM College of Pharmacy, Chinniampalayam Pudur, Jambai Village, Bhavani Taluk, Erode District, Tamil Nadu – 638312, India.

[3] Professor and Head of the Department, Department of Pharmacy, Annamalai University, Chidambaram, Tamil Nadu – 608002, India.

[4] Emeritus Cardiologist, Immanuel Arasar College of Pharmacy, Edavilagam, Nattalam, Marthandam, Tamil Nadu 629195, India.

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Abstract

An attempt was made to formulate, evaluate and commercialize Doxepin Hydrochloride orally disintegrating tablets 3 mg, 6 mg, 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg. A direct blending and compression process by scale-up and scale-down approach / dose-proportional approach was followed to make the product. The excipients include 55% of Pearlitol Flash (Co-processed excipient of 80% D-Mannitol & 20% Maize Starch), 18% of Ludipress (Co-processed excipient of 93% Lactose Monohydrate, 3.5% Povidone K30 & 3.5% Polyplasdone XL), 0.2% of Peppermint Flavor 501500 TP0504, 0.4% of Sucralose and 1.4% of Magnesium Stearate. The composition and process was optimized as per IIG[1] and SUPAC IR guidance document[2]. The final product exhibited rapid disintegration time complying with CDER's guidance on orally disintegrating tablets[3]. The organoleptics of the final product was found acceptably flavored, exhibited smooth mouth feel and tasted pleasantly. Doxepin Hydrochloride is a BCS Class I drug (High Soluble and High Permeable) and accordingly the formulated ODT exhibited rapid disintegration and dissolution profile and hence qualifies for Bio-waiver[4,5] The manufactured product was packed in both multi-dose bottle pack and special child lock enabled push-through provisioned unit dose amber colored PVC – ACLAR blister pack. The packed product was found to be stable for 6 months in ICH recommended accelerated stability storage condition at 40°C / 75%RH, hence qualifies for 2 years shelf life period at room temperature condition. The designed product was successfully commercialized under brand name **InnAR-PZ™** and found to be a cost-effective and differentiated alternative to tablet, capsule & oral liquid concentrate available in the market.

Keywords: Doxepin, co-processed excipients, direct blending, compression, orally disintegrating tablet

*Address for Correspondence:

Packiaraj Jeyachandran Manohari, Vice President – Research & Development and Business Development, Hibrow Healthcare Pvt Ltd and Nutrimed Lifesciences Private Limited, Survey No 258, Thiruvandavar Village Sirupinayur Panchayat, Uthiramerur Taluk, Chennai, Tamil Nadu – 603308, India.

INTRODUCTION

Doxepin Hydrochloride API was first synthesized in Germany in 1963. Doxepin Hydrochloride as a drug product was introduced into the market in 1969[6]. The drug and its product(s) are available in the market for about 55 years. The drug is used for multitude indications viz anti-depression[7], insomnia management[7], anti-viral activity[8], oral Mucositis control and its pain management[9], anti-inflammatory[10], anti-pruritic[11], tinnitus reduction[12], analgesic acitivity[13], anti-histaminic[14], anxiolytic[15], visual hallucination reduction[16], for systemic allergic dermatitis[17], prostate cancer[18], depressive neurosis[19], for generalized anxiety disorder[20], as local anaesthetic[21], treatment of detrusor overactivity in females[22], for atopic eczema[23], anti seizure[24], anti mania[25], management of advanced cancer pain[26], management of fibromyalgia[27], for opiate withdrawal syndrome[28], for smoking cessation[29], for cluster headache[30]etc. In USA market, Doxepin Hydrochloride is available in 3 mg and 6 mg strengths for oral administration as uncoated immediate release tablets under brand name SILENOR® [Distributed by:

Currax™ Pharmaceuticals LLC Morristown, NJ 07960 USA] indicated for adults who have trouble staying asleep. The tablets are packed in white high density polyethylene (HDPE) bottle with child resistant closure (CRC) of 30 tablets count per bottle recommended to be stored at controlled room temperature 20° - 25°C (68° - 77°F), protected from light. The inactive ingredients used in the tablet include microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate. The 3 mg tablet also contains FD&C Blue No. 1. The 6 mg tablet also contains FD&C Yellow No. 10 and FD&C Blue No. 1. SILENOR 3 mg tablets are oval shaped, blue, identified with debossed markings of "3" on one side and "SP" on the other. SILENOR 6 mg tablets are oval shaped, green, identified with debossed markings of "6" on one side and "SP" on the other. The average price of SILENOR® tablet is 115.75 $ for 30 tablets.[31]

Apart from Tablet dosage form, Doxepin Hydrochloride is also available in 10 mg, 25 mg, 50 mg, 75 mg, 100 mg & 150 mg strengths for oral administration as immediate release capsules [Reference Standard Capsules of 150 mg strength was distributed by: Par Pharmaceutical Chestnut Ridge, NY 10977 U.S.A & Reference Standard Capsules for rest of the strengths was distributed by. Mylan Pharmaceuticals Inc. Morgantown, WV 26505 U.S.A] indicated for Psychoneurotic patients with depression and/or anxiety. Depression and/or anxiety associated with alcoholism (not to be taken concomitantly with alcohol). Depression and/or anxiety associated with organic disease (the possibility of drug interaction should be considered if the patient is receiving other drugs concomitantly). Psychotic depressive disorders with associated anxiety including involutional depression and manic-depressive disorders. The target symptoms of psychoneurosis that respond particularly well to doxepin include anxiety, tension, depression, somatic symptoms and concerns, sleep disturbances, guilt, lack of energy, fear, apprehension and worry. Clinical experience has shown that doxepin is safe and well tolerated even in the elderly patient. Owing to lack of clinical experience in the pediatric population, doxepin is not recommended for use in children under 12 years of age. The capsules are packed in white high density polyethylene (HDPE) bottle with child resistant closure (CRC) of 30, 50, 100, 500 & 1000 counts each per bottle recommended to be stored at 20° - 25°C (68° - 77°F), See USP Controlled Room Temperature.[32]

The inactive ingredients used in the MYLAN's product range include colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, pregelatinized starch (corn) and sodium lauryl sulfate. The empty gelatin capsule shells contain D&C Yellow No. 10, gelatin, sodium lauryl sulfate and titanium dioxide. In addition, the 10 mg, 25 mg and 50 mg empty gelatin capsule shells contain FD&C Yellow No. 6 and the 75 mg and 100 mg empty gelatin capsule shells contain FD&C Green No. 3. The imprinting ink contains black iron oxide, D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, propylene glycol and shellac glaze. Mylan's Doxepin Hydrochloride Capsules, USP are available containing doxepin hydrochloride, USP equivalent to 10 mg, 25 mg, 50 mg, 75 mg and 100 mg of doxepin. The 10 mg capsule is a hard-shell, gelatin capsule with a buff opaque cap and buff opaque body axially printed with MYLAN over 1049 in black ink on both the cap and the body. The 25 mg capsule is a hard-shell, gelatin capsule with an ivory opaque cap and white opaque body axially printed with MYLAN over 3125 in black ink on both the cap and the body. The 50 mg capsule is a hard-shell, gelatin capsule with an ivory opaque cap and ivory opaque body axially printed with MYLAN over 4250 in black ink on both the cap and the body. The 75 mg capsule is a hard-shell, gelatin capsule with a brite lite green opaque cap and brite lite green opaque body axially printed with MYLAN over 5375 in black ink on both the cap and the body. The 100 mg capsule is a hard-shell, gelatin capsule with a brite lite green opaque cap and white opaque body axially printed with MYLAN over 6410 in black ink on both the cap and the body. The average price of 30's count per bottle of Mylan's capsules is 15.5 $ for 10 mg, 16.9 $ for 25 mg, 18.7 $ for 50 mg, 26.9 $ for 75 mg, 27.6 $ for 100 mg strength capsules.[33]

The inactive ingredients used in the Par's product range include corn starch, D&C Yellow #10, FD&C Blue #1, FD&C Blue #2, FD&C Red #40, gelatin, magnesium stearate, pharmaceutical glaze, sodium lauryl sulfate, synthetic black iron oxide, titanium dioxide. Doxepin HCl capsules USP, equivalent to 150 mg of doxepin are buff opaque/buff opaque capsules, imprinted "Par 222" on both body and cap. The average price of 30's count per bottle of Par's capsules is 49.5 $ for 150 mg strength capsule.[34]

In US market, apart from tablets and capsules, Doxepin Hydrochloride is also available as oral solution containing doxepin hydrochloride equivalent to 10 mg of doxepin per mL distributed by Lannett Company, Inc. Philadelphia, USA. Indicated for disease condition as mentioned for Doxepin Hydrochloride capsules. Doxepin Hydrochloride Oral Solution USP (Concentrate) is available in 120 mL bottles with an accompanying dropper calibrated at 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg. Each mL contains doxepin hydrochloride equivalent to 10 mg doxepin. Immediately prior to taking this medication, dilute each dose with approximately 120 mL (4 ounces) of water, whole or skimmed milk, or orange, grapefruit, tomato, prune or pineapple juice. Doxepin Hydrochloride Oral Solution USP (Concentrate) is not physically compatible with a number of carbonated beverages. For those patients requiring antidepressant therapy who are on methadone maintenance, Doxepin Hydrochloride Oral Solution USP (Concentrate) and methadone syrup can be mixed together with Gatorade®, lemonade, orange juice, sugar water, Tang® or water, but not with grape juice. Preparation and storage of bulk dilutions is not recommended. Recommended to be stored at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. The inactive ingredients include glycerin; methylparaben; peppermint flavor; propylparaben; water. May contain

hydrochloric acid and/or sodium hydroxide. The average price per bottle of oral solution is 25.12 $.[35]

In India, Doxepin Hydrochloride is available in tablet and capsule. In capsule dosage form, Doxepin Hydrochloride is available in 10 mg and 25 mg strengths in strip packing of 10 capsules / strip under brand name SPECTRA and each strip costs about 78 ₹ for 10 mg strength and 141 ₹ for 25 mg strength[36]. In tablet dosage form, Doxepin Hydrochloride is available in 10 mg in strip packing of 10 tablets / strip under brand name DOX and each strip costs about 30 ₹[37].

Problem Statement, Objective and Scope for Research

Since Doxepin Hydrochloride is a Central Nervous System (CNS) active drug indicated for various diseases with majorly CNS disorders as outlined in the Introduction section – there is a dire market need in delivering the drug to the patients which will make them feel comfortable, convenient and compliant to the physician prescription. Hence in this research one of the objectives is to formulate the Doxepin Hydrochloride into an orally disintegrating tablet which doesn't need any 'water' - for dilution (as like for Doxepin oral solution) or during administration (as like for Doxepin tablet & capsule) and will be convenient for patients who are bed-ridden; with impaired consciousness; non-cooperating; temperamental; physically & mentally retarded as well as weak due to underlying disease condition. The second objective is for the Physician convenience in right dose adjustment (for doxepin oral solution dosing - water and dosing device needed) & dose strength flexibility options (in doxepin tablet - strengths higher than 6 mg not available and in doxepin capsule – strengths lower than 10 mg not available) according to individual patient needs. To achieve this aspect, in this research Doxepin hydrochloride orally disintegrating tablets (ODT) shall be designed encompassing all possible strengths available in the market viz. 3 mg, 6 mg, 10 mg, 25 mg, 50 mg, 75 mg, 100 mg and 150 mg. The physico-chemical characteristics and drug release profile of the designed product shall be compared against the relevant reference standards (RS) from US market. Since it's a new formulation, it will be evaluated for organoleptics and stability. The composition and process involved in making the product shall be suitably optimized to gain confidence for scaling-up into commercial manufacturing. The real scope of research lies in the qualitative and quantitative level of non-drug ingredients (excipients) in the composition to design the ODT to achieve the aforementioned objectives as well as offering the product at a cost-effective pricing.

MATERIALS AND METHODS

Doxepin Hydrochloride from Teva; Pearlitol Flash from Roquette; Ludipress from BASF; Sucralose from JK Sucralose; Peppermint flavor 501500 TP0504 from Firmenich; Magnesium Stearate (Hyqual) from Avantor Performance Materials. All other reagents, salts, solvents used are of analytical grade.

Doxepin Hydrochloride, Doxepin Hydrochloride Capsules, Doxepin Hydrochloride Oral Solution are official in United States Pharmacopoeia (USP). The Assay, Related Substance & Dissolution methods mentioned in the compendial monograph is suitably adopted for the analysis. All other general testing methods viz. Solubility measurements, Particle Size Distribution by Laser Diffraction, Alpine Air Jet Sieve Analysis, Particle Size Distribution by Sieve Analysis, Bulk density, Tapped density, Compressibility Index, Hausner Ratio, Angle of Repose, % LOD, Water by Kf, pH, Microbial Enumeration Testing was done as per USP general chapter.

EXPERIMENTATION, RESULTS AND DISCUSSION

Doxepin Hydrochloride API Characterization

The API was characterized with respect to solubility, solution stability, density, flow property, compressibility, particle size analysis and moisture content analysis through water by kf. The details are provided in the table 1-4 below.

Table 1: Doxepin Hydrochloride API – Solubility & Solution Stability

Solubility & Solution Stability			
Media	mg / mL		
	T0 hrs	T24 hrs	T48 hrs
Water	544	504	568
0.1N HCl	520	513	547
pH 4.5 Acetate Buffer	517	504	504
pH 6.8 Phosphate Buffer	527	525	498
pH 8.5 Borate Buffer	0.5	0.5	0.52

From the above solubility data it's evident that Doxepin Hydrochloride is highly soluble across physiological pH range. Also the solution stability of the API is intact for about 48 hours.

Table 2: Doxepin Hydrochloride API – Density, Flow Property & Compressibility

Bulk Density g / mL	Tapped Density g / mL	Carr's Index %	Hausner Ratio
0.25	0.33	24	1.3

The above density data shows Doxepin Hydrochloride API exhibits fair densification, compressibility & flow characteristics required for a direct blending and compression process.

Table 3: Doxepin Hydrochloride API – Particle Size Distribution

Alpine Air Jet Sieve in microns	% Pass Through
38	95
53	97
125	100

The particle size distribution of Doxepin Hydrochloride API by Alpine Air Jet Sieve analysis revealed 90% of particles are less than 38 micron size. Though the particle are finer, from the density data it's evident that there is less interparticulate friction and the API sufficiently allows air to move through it (Permeability) and also the particles are dense enough to support the direct blending and compression process.

Table 4: Doxepin Hydrochloride API – Moisture Content (Water by Kf)

Test	Result
Water by KF	0.08

Doxepin Hydrochloride API inherently possess very less moisture / water activity and is evident from the Water by Kf testing. As per Doxepin Hydrochloride API specification from API manufacturer the maximum limit for moisture content is 0.5%. Even though the API has less moisture content it is not relevance since the API exhibits good densification, packing and compressibility characteristics as perceivable from density data.

Brand Product Details

The brand product details include brand name, manufactured by, dosage form, strength, disintegration time and dissolution testing. The details presented in the table 5 below,

Table 5: Brand product details

Doxepin Hydrochloride Tablet				
Brand Name	SILENOR®			
Company	Currax™ Pharmaceuticals LLC Morristown, NJ 07960 USA			
Dosage form	Uncoated Immediate Release Tablet			
Strength	3 mg & 6 mg			
Disintegration Time	3 mg & 6 mg Tablet: 2-3 minutes			
Dissolution[38] (USP-II (Paddle), 50 RPM, 500 mL, 0.1N HCL	**Time min =>**	**10**	**15**	**30**
	3 mg strength			
	Mean	91	100	100
	Range	89-92	99-100	99-100
	%RSD	1.68	0.58	0.58
	6 mg strength			
	Mean	93	98	100
	Range	91-95	97-100	98-100
	%RSD	2.15	1.55	1.16
Doxepin Hydrochloride Capsule				
Brand Name	Doxepin Hydrochloride Capsules			
Dosage form	Hard gelatin capsules			
Strength	10 mg, 25 mg, 50 mg, 75 mg & 100 mg			
Company	Mylan Pharmaceuticals Inc. Morgantown, WV 26505 U.S.A			
Strength	150 mg			
Company	Par Pharmaceutical Chestnut Ridge, NY 10977 U.S.A			
Disintegration Time	10 mg, 25 mg, 50 mg, 75 mg, 100 mg & 150 mg: 3-6 minutes			
Dissolution[38] (USP-I (Basket), 100 RPM, 500 mL,	**Time min =>**	**10**	**15**	**30**

0.1N HCL	**10 mg strength**			
	Mean	49	87	100
	Range	39-51	82-90	98-101
	%RSD	13.88	4.68	1.53
	25 mg strength			
	Mean	44	86	100
	Range	33-46	81-91	99-100
	%RSD	17.07	5.81	0.58
	50 mg strength			
	Mean	39	85	101
	Range	28-41	80-92	100-102
	%RSD	19.44	7.04	0.99
	75 mg strength			
	Mean	34	84	100
	Range	23-36	79-89	100-101
	%RSD	22.58	5.95	0.58
	100 mg strength			
	Mean	32	83	99
	Range	21-34	78-89	99-100
	%RSD	24.14	6.61	0.58
	150 mg strength			
	Mean	25	81	100
	Range	14-27	75-87	99-101
	%RSD	31.82	7.41	1.00

From the above tabulated information it's clear that the marketed Doxepin Hydrochloride formulation as tablet and capsules exhibit rapidly dissolving dissolution pattern across the strengths. Except the initial time point (in case of capsules), the unit-to-unit variation as perceived from %RSD (Relative Standard Deviation) is very controlled and minimal. Hence the development of the orally disintegrating tablets to be done to exhibit rapid disintegration and dissolution profile to match with the Quality Target Product Profile (QTPP) - Marketed brand product characteristics.

Excipient Selection Rationale & Drug – Excipient (D-E) Compatibility Study

As part of formulation approach, based on the API and Brand product characterization it was decided to keep the composition simple and effective. For ODT design, Co-processed excipients viz. Pearlitol Flash and Ludipress were chosen as diluents, Peppermint flavor as flavorant, Sucralsoe as sweetener and Magnesium Stearate as lubricant. Further to check on the suitability of selected excipients it was decided to perform the drug – excipient compatibility study. The possibility of drug-excipient interaction was investigated by HPLC analysis. Study was conducted by preparing homogenous mixture of excipient with drug filled in glass vials were exposed to 40 ± 2°C / 75 ± 5%RH and 60°C for 4 weeks and 2 weeks respectively. Samples were analyzed for Assay, Total Impurity, Water By Kf and the results are provided in table 6 below,

Table 6: Drug-Excipient Compatibility Study

API + Excipients	Tests	Initial	Duration / Storage Conditions		
			2nd Week 55 °C	2nd Week 40°C/75%RH	4th Week 40°C/75%RH
Doxepin Hydrochloride	AY, %	99.86	100.17	99.39	99.92
	TI, %	0.042	0.043	0.045	0.048
	WKf,%	0.08	0.08	0.12	0.11
Doxepin Hydrochloride + Ludipress	AY, %	99.32	99.88	99.70	99.36
	TI, %	0.057	0.345	0.060	0.054
	WKf,%	2.95	2.14	2.65	2.32
Doxepin Hydrochloride + Pearlitol Flash	AY, %	98.34	98.44	98.68	98.76
	TI, %	0.073	0.914	0.112	0.138
	WKf,%	1.42	1.33	1.35	1.32
Doxepin Hydrochloride + Magnesium Stearate (Hyqual)	AY, %	100.83	100.85	100.23	100.32
	TI, %	0.047	0.081	0.055	0.057
	WKf,%	0.70	0.86	0.78	0.68
Doxepin Hydrochloride + Peppermint Flavor 501500 TP0504	AY, %	98.50	99.69	98.16	99.30
	TI, %	0.056	0.050	0.046	0.045
	WKf,%	2.85	2.83	2.11	2.83
Doxepin Hydrochloride + Sucralose	AY, %	100.26	99.72	99.41	99.12
	TI, %	0.050	0.707	0.082	0.118
	WKf,%	1.38	1.29	1.04	1.76

From the presented D-E study results, the excipient selection for the formulation holds good there is neither significant drop in Assay nor significant increase in Total impurity and Water by Kf numbers from the Initial point. Hence the excipients are found compatible to Doxepin HCl API.

Development Pharmaceutics of Doxepin HCl Orally Disintegrating Tablets

While finalizing the unit composition details, the level of organoleptic excipients viz. Sucralose and Peppermint flavor was finalized based on flavor principle perceived (hedonic) in-terms of Pleasant / Intense / Under-flavoring and the sweetness level (taste of ODT while remaining in buccal cavity before swallowing and residual after-taste post swallowing) of the product were tested and feed-back obtained from willing volunteers. The level of lubricant, Magnesium Stearate was selected based on the ease of tabletting process as well as surface characteristics of manufactured ODT i.e. without sign of any physical defects viz. Picking, Sticking, Striation (Die Wall Corrosion) while tabletting. The diluent ratio of Pearlitol Flash to Ludipress was selected based on the blend flow (angle of repose), binding during tabletting (hardness range achievability & friability), disintegration time (DT), organoleptic mouth feel (smooth or coarse nature of ODT residues in buccal cavity after administration) and dissolution comparability with the marketed brand product. The unit composition finalized across the strengths of Doxepin HCl ODT is as follows in table 7,

Table 7: Composition of Doxepin HCl ODT

Ingredients	mg per tablet							
Doxepin HCl	3.00	6.00	10.00	25.00	50.00	75.00	100.00	150.00
Pearlitol Flash	6.60	13.20	22.00	55.00	110.00	165.00	220.00	330.00
Ludipress	2.16	4.32	7.20	18.00	36.00	54.00	72.00	108.00
Peppermint Flavor 501500 TP0504	0.02	0.05	0.08	0.20	0.40	0.60	0.80	1.20
Sucralose	0.05	0.10	0.17	0.40	0.80	1.20	1.60	2.40
Magnesium Stearate (Hyqual)	0.17	0.34	0.57	1.40	2.80	4.20	5.60	8.40
Tablet Weight	**12.00**	**24.00**	**40.00**	**100.00**	**200.00**	**300.00**	**400.00**	**600.00**
Diameter in mm for Round Flat Faced Bevel Edged Punch Tooling	1.5	3	5	7.5	8.5	9.5	10.5	12

The manufacturing process involved sifting Pearlitol Flash, Ludipress, Peppermint flavor and Sucralose through # 30 ASTM mesh and divided into two equal parts. Doxepin HCl was sifted through #30 ASTM mesh. In the double cone blender, the sifted Doxepin HCl was sandwiched between 2 parts of excipient blend and blended for 10 minutes at 15 revolutions per minute (RPM). The whole blended material was sifted through # 30 ASTM mesh and again blended in double cone blender at 15 RPM for 10 min. Finally Magnesium Stearate was sifted through # 40 ASTM mesh and blended along with the bulk of the blend in double cone blender at 15 RPM for 5 min. The composition and final blend manufacturing process was designed by dose proportional approach or scale-up and scale-down approach. Since the manufacturing involved usage of excipients which are Co-processed ready-made blend (Ludipress and Pearlitol Flash) it is recommended to perform the process from dispensing to packing under de-humidified condition viz. 25 ± 2°C and 40 ± 5%RH. By making the blend for the highest strength, the blend for all other strengths can be derived from it. The final blend was characterized with respect to Description, Smell, Taste, Particle Size Distribution (by Sieve Analysis), Bulk density, Tapped density, Carr's index, Hausner ratio, Water by Kf and Angle of repose the details are presented in table 8,

Table 8: Evaluation of Blend for compression

Bulk density (g / mL)	0.52	**Tapped density (g / mL)**		0.66	**Carr's Index (%)**	21	**Hausner Ratio**	1.27	**Angle of Repose (°)**	25
Water by Kf (%)	3.3	**Description**		White to off-white free flowing powder			**Flavor**	Mint flavored	**Taste**	Agreeably sweet
Particle Size Distribution	**ASTM Sieve #**	20	30	40	60	80	100	140	200	Pan
	% Retained	0	0	14	22	10	13	13	19	11

The total presence of API in the final blend for compression across the strength is 25%. When comparing the density, compressibility index, hausner number of final blend vis a vis the API characteristics there is a definite improvement in densification and compressibility attributes. The angle of repose gives confidence in pursuing the blend for a direct compression process. Moisture content and description evaluation of the blend is for information pupose only but can be used to investigate any change in the physico-chemical characteristics of the blend if kept on hold for a considerable period of time before compression! From the PSD data its clearly evident that the excipients have improved on the granular fractions of the blend to improve the flow, air permeability, compressibility and binding nature of the blend. The granules to fines fraction that can be inferred from the PSD data is 46 to 54 which is reasonable enough to qualify the manufacturing process design for a direct blending and compression process.

Based on the composition details mentioned in table 7, the Critical Material Attributes (CMA) from Quality by Design (QbD) view point was identified based on QTPP, initial risk assessment and preliminary prototype trials. Firstly, the Doxepin HCl API particle size distribution is crucial to achieve comparable drug release characteristics to the brand product and also influences

the composition and process selection for designing the ODT. Hence the specification for the incoming API PSD from API manufacturer was fixed as d90 by Malvern Mastersizer measurement to be less than 50 microns or 100% pass through 53 microns mesh when done by Alpine Air Jet Sieve Analysis technique. Secondly, the diluent amount especially the ratio of Pearlitol Flash to Ludipress and needs to be maintained at 75:25 for good binding / compressibility, less friability, rapid disintegration time, smooth mouth feel and good blend flow characteristics. Thirdly, the grade of Magnesium Stearate used and it must be non-bovine grade and be a vegetable grade source to avoid PRION infection in patients and to make the end-product qualify for absence of Transmissible Spongiform Encephalopathy (TSE) / Bovine Spongiform Encephalopathy (BSE). And also the Specific Surface Area (SSA in m^2/g) of the incoming Magnesium Stearate from the excipient manufacturer to be between 5.0-10.0 so that the lubrication efficiency is at par and allows for trouble-free compression or tabletting process of ODT without any physical defects.

As part of manufacturing process optimization, as a 1st step - blend uniformity study was taken up in the highest strength, 150 mg [Across the strengths the % of API in the composition is 25%] in 2 stages viz. the blending stage before addition of the lubricant (Prelubrication) and the blending stage after addition of the lubricant (Lubrication). This is important to ensure homogenous distribution of Doxepin HCl API in the final blend. In the prelubrication stage, blending was done at 15 RPM for 3 different time intervals viz. 5 minutes, 10 minutes and 15 minutes. In the lubrication stage, blending was done at 15 RPM for 3 different time intervals viz. 4 minutes, 5 minutes and 6 minutes. At each time point from the blender, blend uniformity samples were collected from 10 different locations[39] using sample thief equipped with relevant cc die. The blend uniformity results are provided in the table 9 below, based on the blend uniformity results obtained one can infer on the uniform distribution of API throughout the blend. On the aspect of blending time point fixation, 10 minutes blending time at 15 RPM was finalized for Prelubrication stage and 5 minutes blending time at 15 RPM was finalized for Lubrication stage.

Table 9: Manufacturing process optimization – Blend Uniformity in Blending Process

Sampling Location in Blender	Blend Uniformity, % Assay					
	Pre Lubrication @ 15 RPM			Lubrication @ 15 RPM		
	5 min	10 min	15 min	4 min	5 min	6 min
1	99.68	99.71	97.60	99.16	96.33	99.75
2	99.50	99.19	97.24	98.71	99.57	99.64
3	99.41	100.02	98.01	98.84	97.05	99.22
4	99.66	99.27	98.63	98.90	97.95	98.59
5	99.26	99.85	98.58	98.12	96.94	99.34
6	99.11	99.80	99.28	99.09	97.78	97.92
7	100.23	99.43	99.00	98.57	98.85	98.78
8	99.41	99.83	98.95	98.57	98.14	99.22
9	100.15	99.02	98.67	99.05	97.82	98.35
10	99.74	99.14	98.68	98.48	97.71	99.54
Average	99.61	99.52	98.46	98.75	97.82	99.04
Minimum	99.11	99.02	97.24	98.12	96.33	97.92
Maximum	100.23	100.02	99.28	99.16	99.57	99.75
% RSD	0.36	0.36	0.66	0.33	0.95	0.61

The second step of optimization was taken up during compression process. In this study, hardness variation effect on thickness, friability, disintegration time and dissolution was studied. Apart from this, tabletting press speed variation effect on content uniformity (%CU) or uniformity of dosage units (UOD) was also studied as per USP. Ideally if the composition of the product is optimized it should lead to limited effect or influence of tablet hardness on disintegration time and tablet press speed on content uniformity of tablets. The mentioned dissolution study in the hardness variation study was done using the composite samples of varying hardness levels to check the influence of hardness variation on drug dissolution and release. The details are provided in the table 10 below,

Table 10: Manufacturing process optimization – Compression or Tabletting Process

Dose mg	Wt mg	Thick mm	Hard kP	Friable %	DT secs	% CU (Mean, Range, %RSD & AV) in Tablet Press Speed		% Dissolution Mean, Range, %RSD		
						15 RPM	30 RPM	10 min	15 min	30 min
3	11 to 13	1.1 to 2.1	0.5 to 1.5	0.2 to 0.6	5 to 10	99 96-102 1.95 4.64	101 97-106 2.45 5.93	99 97-100 1.55	99 99-100 0.58	100 100-101 0.58
6	24 to 25	1.3 to 2.6	0.5 to 2	0.2 to 0.6	5 to 10	100 99-101 0.72 1.75	101 98-106 2.33 5.65	98 95-98 1.79	99 97-100 1.55	100 99-100 0.58
10	38 to 41	1.6 to 2.1	0.5 to 2.5	0.1 to 0.5	5 to 10	99 98-101 1.54 3.74	100 98-100 1.16 2.81	99 99-100 0.58	98 98-99 0.59	100 99-101 1.00
25	99 to 101	2.3 to 2.5	1 to 4	0.1 to 0.4	5 to 15	98 95-101 1.67 4.60	99 96-100 1.34 3.17	97 96-98 1.03	98 98-99 0.59	101 100-101 0.57
50	198 to 200	2.6 to 2.8	2 to 5	0.1 to 0.4	5 to 15	99 96-103 2.15 5.09	101 99-103 1.12 2.72	96 95-97 1.04	98 97-98 0.59	99 99-100 0.58
75	299 to 301	3.2 to 3.4	2 to 5	0.1 to 0.5	10 to 20	99 97-100 1.01 2.40	95 94-96 0.64 5.25	95 94-95 0.61	98 96-98 1.19	99 98-99 0.59
100	397 to 402	3.5 to 3.8	3 to 7	0.2 to 0.5	10 to 20	98 96-98 1.19 2.60	99 98-100 1.04 2.40	94 94-95 0.61	96 96-97 0.60	100 98-101 1.53
150	599 to 603	4.3 to 4.6	3 to 8	0.2 to 0.6	10 to 20	97 96-99 1.57 4.65	98 98-100 1.17 2.50	92 91-93 1.09	97 95-97 1.20	99 97-100 1.55

In the above tabulated information strength of the tablet is mentioned as dose; ODT's weight range observed during tabletting process is mentioned as Wt; ODT's thickness range observed during tabletting process is mentioned as Thick; ODT's hardness range observed during tabletting process is mentioned as Hard; ODT's % friability observed during tabletting process across the hardness range is mentioned as % friable; ODT's disintegration time observed during tabletting process across the hardness range is mentioned as DT; The dissolution testing was conducted in USP-II (Paddle), 50 RPM, 500 mL, 0.1N HCL. %CU or UOD was determined

for 10 units at 2 different RPM of tabletting machine speed to check on the machine speed influence on API uniformity in tablets. The data presented shows rapid disintegration time (in-line to CDER Guidance on ODT) and dissolution of ODT's manufactured across strengths and the profile is comparable to the marketed brand product in the form of Tablets and Capsules. For the dissolution comparison, 'f1f2' was not calculated to determine the similarity since the data-sets doesn't fulfill the perquisites for the statistical treatment[40]. The dissolution data of the manufactured ODT also fulfills the ICH requirement of BCS Class I drug and exhibits rapid dissolution profile and hence qualifies for Bio-waiver (No need of Bio-equivalence). The finalized composition is optimized with respect to the level of excipients in the formulation which is evident from the hardness achievability, hardness independent disintegration time and dissolution across the strengths. The formulated ODT has sufficient physical strength to withstand the stress during bottle and blister packing as inferred from the % Friability data. The final blend for compression can be conveniently compressed into ODT with appropriate toolings for all the strengths in double rotary tablet press at a machine speed of up to 30 RPM. This is possible since the Acceptance Value (AV) obtained from the %CU or UOD data complies with the USP requirement of less than 15. Also the %RSD (Relative Standard Deviation / Coefficient of Variance) data of the sample is well controlled indicating less variability in the drug content.

The manufactured ODT was packed in both Multi-dose and Unit-dose configuration. Multi-dose configuration involve packing of 50 ODT's per bottle of 10 cc (for 3 mg), 25 cc (for 6 mg), 50 cc (for 10 mg), 75 cc (for 25 mg), 100 cc (for 50 mg), 150 cc (for 75 mg), 200 cc (for 100 mg), 250 cc (for 150 mg) - White HDPE bottle with Polypropylene Child Resistant Closure with induction seal lined; cotton coil was included within the bottle as a dunnage along with the product – this provision is done to prevent ODT breakage due to rattling while handling or transportation; Also one (1) number of 1 g silica gel pouch was added into the bottle as desiccant – the reason being, ODT is manufactured using dry process (direct blending and compression) using excipients of co-processed nature hence there is a chance of softening of ODT on storage due to moisture absorption by the product from air within the void space of the bottle. Unit-dose configuration involves packing of 21 ODT's per blister pack. The blister pack's material of construction (MOC) involves Base foil containing Polyvinyl Chloride (PVC)-ACLAR (Poly-Chloro-Tri-Fluoro-Ethylene (PCTFE) and the lidding foil containing Aluminum backing. The blister pack was provided with features viz. "tamper-evident" - decreased chance of tampering-with and medication errors. Each individual blister pocket is accurately labeled with the correct drug and strength, as well as lot number and expiration date; "child-resistant peelable foil" – is a significant innovation in packaging to prevent cases of unintentional poisoning in children at the same time allowing the elderly to get access to their medicines. Simply, the child-resistant packaging design is that it should be easy for the elderly and hard for children to open the packing and access the medicine; "perforation feature" – this enables to tear-off one single dose from the pack. This feature prevents the injuries like small cuts / abrasion to one's hand or fingers while handling / opening the blister pack. The following table 11 elaborates on the stability data of the product packed in 2 different configurations and exposed as per ICH recommended[41] storage condition of 40°C / 75%RH for 6 months.

Table 11: Stability of Doxepin HCl ODT in @ 40°C / 75%RH for 6 months in 2 different packs

Strength mg	Pack	Assay %	WKf %	FOD[42]	DT secs	RS		% Dissolution Mean, Range, %RSD		
						%HUI	%TI	10 min	15 min	30 min
3	Initial	100.1	3.1	Pass	5-10	0.04	0.23	99 97-100 1.55	99 99-100 0.58	100 100-101 0.58
	Bottle	98.3	3.4	Pass	10-15	0.09	0.52	97 96-99 1.57	100 98-101 1.53	99 98-100 1.01
	Blister	99.2	3.2	Pass	5-10	0.06	0.35	98 97-101 2.11	99 98-100 1.01	99 97-100 1.55
6	Initial	99.8	3.2	Pass	5-10	0.03	0.21	98 95-98 1.79	99 97-100 1.55	100 99-100 0.58

	Bottle	98.7	3.5	Pass	10-15	0.1	0.70	97 95-98 1.58	100 98-101 1.53	99 98-100 1.01
	Blister	99.1	3.3	Pass	5-10	0.07	0.49	99 97-100 1.55	99 98-101 1.54	99 97-101 2.02
10	Initial	100	3.2	Pass	5-10	0.04	0.22	99 99-100 0.58	98 98-99 0.59	100 99-101 1.00
	Bottle	98.4	3.5	Pass	10-15	0.09	0.60	98 98-99 0.59	99 98-100 1.01	100 99-100 0.58
	Blister	99.1	3.3	Pass	5-10	0.07	0.41	99 99-100 0.58	100 99-100 0.58	100 99-101 1.00
25	Initial	101.1	3.2	Pass	5-15	0.04	0.24	97 96-98 1.03	98 98-99 0.59	101 100-101 0.57
	Bottle	97.9	3.4	Pass	10-15	0.11	0.66	97 95-98 1.58	98 96-99 1.56	98 97-101 2.11
	Blister	100.8	3.3	Pass	10-15	0.07	0.42	99 97-100 1.55	99 97-101 2.02	100 98-100 1.16
50	Initial	100.4	3.3	Pass	5-15	0.05	0.23	96 95-97 1.04	98 97-98 0.59	99 99-100 0.58
	Bottle	98.1	3.6	Pass	10-15	0.08	0.37	97 96-99 1.57	98 96-100 2.04	100 98-101 1.53
	Blister	99.7	3.4	Pass	10-15	0.07	0.32	98 97-99 1.02	98 98-100 1.17	99 98-100 1.01
75	Initial	101	3.1	Pass	10-20	0.04	0.22	95 94-95 0.61	98 96-98 1.19	99 98-99 0.59
	Bottle	98.6	3.4	Pass	15-20	0.09	0.50	94 92-95 1.63	97 95-100 2.59	101 98-101 1.73
	Blister	99.5	3.1	Pass	10-20	0.05	0.28	96 95-98	98 96-100	100 99-101

								1.59	2.04	1.00
100	Initial	101	3.4	Pass	10-20	0.04	0.23	94 94-95 0.61	96 96-97 0.60	100 98-101 1.53
	Bottle	97.9	3.6	Pass	15-25	0.1	0.58	93 92-94 1.08	97 95-98 1.58	99 96-100 2.12
	Blister	99.4	3.4	Pass	15-20	0.06	0.35	94 92-97 2.67	98 96-100 2.04	99 98-101 1.54
150	Initial	100.8	3.3	Pass	10-20	0.05	0.24	92 91-93 1.09	97 95-97 1.20	99 97-100 1.55
	Bottle	98	3.6	Pass	15-25	0.11	0.53	89 87-92 2.82	96 94-98 2.08	101 98-101 1.73
	Blister	99.9	3.4	Pass	15-20	0.08	0.38	93 91-94 1.65	99 97-100 1.55	99 98-100 1.01

Based on the 6 months accelerated stability data, Doxepin HCl ODT was found to be stable and effective in both bottle and blister packs. There is no significant excursion observed in Assay value (90%-110%); Water by Kf (WKf) value (Not More Than 5%); Fineness of Dispersion (FOD) - The fineness of dispersion test according to the Eur. Pharm. 7.0 was performed by taking two (2) tablets in a beaker with 100 mL of distilled water, and stirred until completely dispersed. Dispersion was poured through a sieve screen 0.7 mm (25 ASTM Sieve). If all the parts passed through the sieve, the tablets passed the test. If there were any remaining particles on the sieve, the tablets failed the test. This test is specifically done to demonstrate the possibility and utility of the manufactured ODT to be administered in solution form in case of emergency or for convenience sake in pediatrics and geriatrics population; Disintegration Time (DT) value (Not More Than 30 seconds); Related Substances (RS) value(s) expressed as Highest Unknown Impurity (Not More Than 0.2%) & Total Impurity (Not More Than 1%); The dissolution testing was done in USP-II (Paddle), 50 RPM, 500 mL, 0.1N HCL. The stability tested samples were found to comply with the specification of NLT 85% dissolved in 15 minutes.

The microbial testing of the manufactured product was not performed since the complete activity from dispensing to packing was done at Relative Humidity (RH) less than 45% hence the water activity (aw) is 0.45 which is not favorable for any microbial growth[43]. Moreover the calculated equilibrium moisture content (EMC) of the ODT composition is about 3%. Inherently the Doxepin HCl API has moisture content of 0.08% only. The manufactured ODT is also packed in bottles with absorbent cotton as dunnage along with 1 g silica gel canister as desiccant and the foil used for the blister packing is PVC- ACLAR which exhibits lower Water Vapor Transmission Rate[44] (WVTR) than other conventional foils viz. PVC, PVDC etc Hence the chance of Microbial growth or content in the manufactured ODT is a very remote possibility. On the Brand name for the manufactured ODT, **InnAR-PZ™** was finalized. The brand name aptly denotes the 'calming affect' function of the product in the affected patients. The product was successfully commercialized and the finer details on R&D and Commercial manufacturing details are compared and presented in table 12,

Table 12: Comparison of R&D Vs Commercial manufacturing of Doxepin HCl ODT

Particulars	R&D	Commercial	Remarks
Batch Size	10,000 Tablets per strength	200,000 Tablets per strength	Common blend / Scale-Up & Scale-Down approach. 20 times increase in batch size from R&D to Commercial scale.
Sifting	Vibrosifter	Vibrosifter	For de-lumping & de-aggregation.
Blending	Double Cone Blender 50 Litres	Double Cone Blender 800 Litres	For pre-lubrication and lubrication.
Compression	Single Rotary 16 Station Tablet Press 480 tablets / minute	Double Rotary 42 Station Tablet Press 2520 tablets / minute	For tabletting.
Bottle Packing	Manual by hand 2 bottles / minute	CVC Bottle Packing Line 100 bottles / minute	For Multi-dose packing.
Blister Packing	Single Blister Packing Machine 5 blister pack / minute	Elmac Blister Packing Line 300 blister pack / minute	For Unit-dose packing.

The cost of Doxepin HCl ODT was compared with national and international brands and presented in table 13. The manufactured product was found cost-effective and would benefit the patient population at large.

Table 13: Costing of Doxepin HCl ODT & comparison with National and International Brand

International Brand (USA) [in $]	National Brand (Within India) [in ₹]	Price of InnAR-PZ™ ODT (Doxepin HCl) [in ₹]
Doxepin HCl Oral Solution Concentrate 120 mL 10 mg / mL Price: 25.12 Doxepin HCl Capsule 30's count bottle 10 mg: 15.5 25 mg: 16.9 50 mg: 18.7 75 mg: 26.9 100 mg: 27.6 150 mg: 49.5 SILENOR® Doxepin HCl Tablet 30's count bottle 3 mg: 115.75 6 mg: 115.75	SPECTRA™ Doxepin HCl Capsules 10 mg 10 capsules / strip Price: 78 SPECTRA™ Doxepin HCl Capsules 25 mg 10 capsules / strip Price: 141 DOX™ Doxepin HCl Tablet 10 mg 10 tablets / strip Price: 30	**50's count bottle pack** 3 mg: 45 6 mg: 85 10 mg: 141 25 mg: 345 50 mg: 680 75 mg: 1005 100 mg: 1350 150 mg: 2000 **21's count blister pack** 3 mg: 20 6 mg: 37 10 mg: 61 25 mg: 149 50 mg: 293 75 mg: 433 100 mg: 581 150 mg: 860

SUMMARY AND CONCLUSION

In this research work, we have successfully developed and commercialized a niche differentiated drug product of Doxepin HCl in the form of Orally Disintegrating Tablets. While adventing this research, the quality target product profile (QTPP) was well defined by doing thorough study of the various drug products of Doxepin HCl available in market both nationally and internationally. Brand product characterization enabled us to identify a definite gap in the market (patient & physician need to be fulfilled) in the form of convenience, ease of administration, dosing flexibility etc. Subsequently, the Doxepin HCl API was sourced after thorough review of drug master file (DMF) details and the API was characterized with respect to solubility, solution stability, density, particle size distribution, flow, compression index and moisture content. From the API characterization data, we have concluded on certain aspects of Doxepin HCl API, viz. BCS Class I drug (High Soluble & High Permeable); API exhibited relevant density, flow, compressibility, moisture content & particle size distribution values suitable for direct blending and compression process. Before proceeding to the formulation aspect, it was decided to perform a risk assessment in the selection of excipients that will enable us to design the formulation by dose-proportional approach or scale-up scale-down approach since the development involved wide range of strengths viz. 3 mg, 6 mg, 10 mg, 25 mg, 50 mg, 75 mg, 100 mg & 150 mg (8 Strengths). Based on prior research experience and having handled wide range of excipients, Pearlitol Flash and Ludipress was finalized as diluent, binder & disintegrant; Peppermint was finalized for flavoring; Sucralose as sweetener and Magnesium Stearate as lubricant. The suitability of selected excipients was further evaluated by performing Drug-Excipient Compatibility study (D-E Study). All the selected excipients were found to be compatible with Doxepin HCl API. Based on prototype formulation trials, formula optimization and organoleptic evaluation, the final composition was finalized which include 55% of Pearlitol Flash (Co-processed excipient of 80% D-Mannitol & 20% Maize Starch), 18% of Ludipress (Co-processed excipient of 93% Lactose Monohydrate, 3.5% Povidone K30 & 3.5% Polyplasdone XL), 0.2% of Peppermint Flavor 501500 TP0504, 0.4% of Sucralose and 1.4% of Magnesium Stearate. The maximum daily dose (MDD) of Doxepin HCl is 300 mg per day. The composition was checked for the IIG compliance and was found to comply with the regulatory requirements. The critical material attribute (CMA) include the particle size of API; density and particle size distribution of Pearliol Flash and Ludipress; specific surface area of Magnesium Stearate. The manufacturing process was optimized with respect to blending (pre-lubrication and lubrication) and compression process (Speed study & Hardness study). The critical process parameter (CPP) includes Blending time (Lubrication) and Compression (Hardness). The critical quality attributes (CQA) identified based on QTPP and ODT dosage form design is Density of blend for compression, Angle of Repose of blend for compression, Particle size distribution of blend for compression, Disintegration Time of ODT, Dissolution of ODT. Thus the whole development pharmaceutics of Doxepin HCl ODT was designed and developed by quality by design (QbD) approach. To improve on the overall quality (including microbial), stability and effectiveness of the product, the whole process from dispensing, manufacturing and packing was done under de-humidified environment (25 ± 2°C and 40 ± 5%RH). The packing configuration – both multi-dose (bottle) and unit-dose (blister) was fine-tuned and finalized with respect to material of construction (MOC of polymer) and MVTR values of the packing material. The manufactured product was found to be stable in the intended packing configuration(s) under ICH recommended accelerated storage condition for 6 months. Also the CQA targets of the manufactured product were found comparable to QTPP (Brand Product performance). Commercially, the developed Doxepin HCl ODT (**InnAR-PZ™**) was found to be cost-effective and would remain competitive and relevant to its objective and utility from patients and physicians view-point.

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