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FORMULATION AND IN-VIVO CLINICAL STUDY OF DULOXETINE HYDROCHLORIDE DELAYED RELEASE CAPSULE BASED ON MUPS TECHNOLOGY AS PER QUALITY BASED DESIGN

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ABSTRACT

Duloxetine Hydrochloride delayed release capsule is indicated to treat depression and anxiety. In addition, duloxetine is used to help relieve nerve pain (peripheral neuropathy) in people with diabetes or ongoing pain due to medical conditions such as arthritis, chronic back pain, or fibromyalgia (a condition that causes widespread pain)[1] The reference listed drug for Duloxetine capsule is 20 mg, 30 mg and 60 mg. We used Quality by Design (QBD) to develop generic Duloxetine Hydrochloride capsule is 20 mg, 30 mg and 60 mg that are therapeutically equivalent to the RLD. Initially, the quality target product profile (QTPP) was defined based on the properties of the drug substance, characterization of the RLD product, and consideration of the RLD label and intended patient population. Identification of critical quality attributed (CQAs) was based on the severity of harm to a patient (safety and efficacy) resulting from failure to meet the quality attribute of the drug product. Our investigation during pharmaceutical development focused on those CQAs that could be impacted by a realistic change to the drug product formulation or manufacturing process. For generic duloxetine hydrochloride capsule, these CQAs included % Assay, Acid resistance, Dissolution, Ethanol Dose Dumping, % Drug released and Degradation products. We have done a clinical Bioequivalence study on both fasting and fed study and had bioequivalence with the innovator.

INTRODUCTION

As per biopharmaceutical classification system (BCS) Duloxetine hydrochloride is a low soluble drug with high permeability i.e. a BCS Class II compound. During the prototype formulation development dissolution conditions were followed as recommended in the "Dissolution database" of USFDA. Dissolution method uses 0.1 N HCl using USP apparatus I (Basket) stirred at 100 rpm with a dissolution volume of 900 ml at a temperature of 37±0.5 ^{0}C for 2 hour followed by pH 6.8 Phosphate buffer using USP apparatus I (Basket) stirred at 100 rpm with a dissolution volume of 900 ml at a temperature of 37±0.5 ^{0}C for 5, 10, 15, 30, 45, 60, 75 and 90 minutes.[2] This research was done with the intension to prepare and evaluate Delayed Release capsule of Duloxetine hydrochloride a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) and used in the treatment of depression, generalized anxiety disorder, and reliefs the pain of fibromyalgia and peripheral neuropathy. It is chemically (+)-(S)-N-methyl-γ-(1-naphthyloxy)-2-thio phenypropyl amine hydrochloride, and its bioavailability is 50%. When duloxetine hydrochloride capsule dissolves in acidic environment of stomach (<pH 3.0; 0.1 N Hydrochloric acid) while administering through oral route, it produces a toxic product called alpha-naphthol. The gastric resistant capsule could be the right choice which is one of the best outcomes of enteric coating technology to prevent the formation of alpha-naphthol and to improve the bioavailability of duloxetine Hydrochloride.[3] The manufacturing process consists of active coating, sub coating, enteric coating, top coating, filling in capsules and packaging. Our report includes both in-process, finished product and stability specification. The manufacturing process and its process parameters will be monitored during the scale up batch of the product and adjustment will be made accordingly. The process will be monitored during the life cycle of product and the additional knowledge gained will be utilized to make adjustments to the specification in In-process, finished product and stability specification as appropriate.

MATERIAL

Duloxetine hydrochloride was purchased from Zhejiang Liaoyuan Pharmaceutical Co., Ltd. Sucrose pellet core 0.50-0.60mm was purchased from Hangzhou Gaocheng

Biological Nutrition Technology Co., Ltd. Hypromellose was purchased from E5 LV Nutrition & Biosciences Corporate Internal, Sucrose was purchased from Jiaxing Bailang Starch Products Co., Ltd. Talcum powder was purchased from Pharma M Imerys Talc Italy, Hypromellose acetate succinate was purchased from AS-LF Shin-Etsu Chemical Industry Co., Ltd. Triethyl citrate was purchase from Bengbu Fengyuan Tushan Pharmaceutical Co., Ltd, Film-coated premixes 03A18452-CN was purchase from Shanghai Colorcon Coating Technology. Concentrated ammonia solution 25%-28% was purchased from Nanjing Chemical Reagent Co., Ltd.

METHOD

The dissolution method recommended in the FDA dissolution method database for this product was utilized 900 ml of 0.1 N HCl using USP apparatus I (Basket) at 100 rpm followed by pH 6.8 Phosphate buffer using USP apparatus I (Basket) at 100 rpm. The temperature of the dissolution media was maintained at 37±0.5°C and the drug concentration were determined using HPLC method. The % drug release of RLD tablets was also obtained at different pH (0.1 N HCl followed by pH 5.5 Acetate buffer, 0.1 N HCl followed by pH 6.0 Phosphate buffer, pH 4.5 Acetate Buffer followed by pH 6.8 Phosphate Buffer).

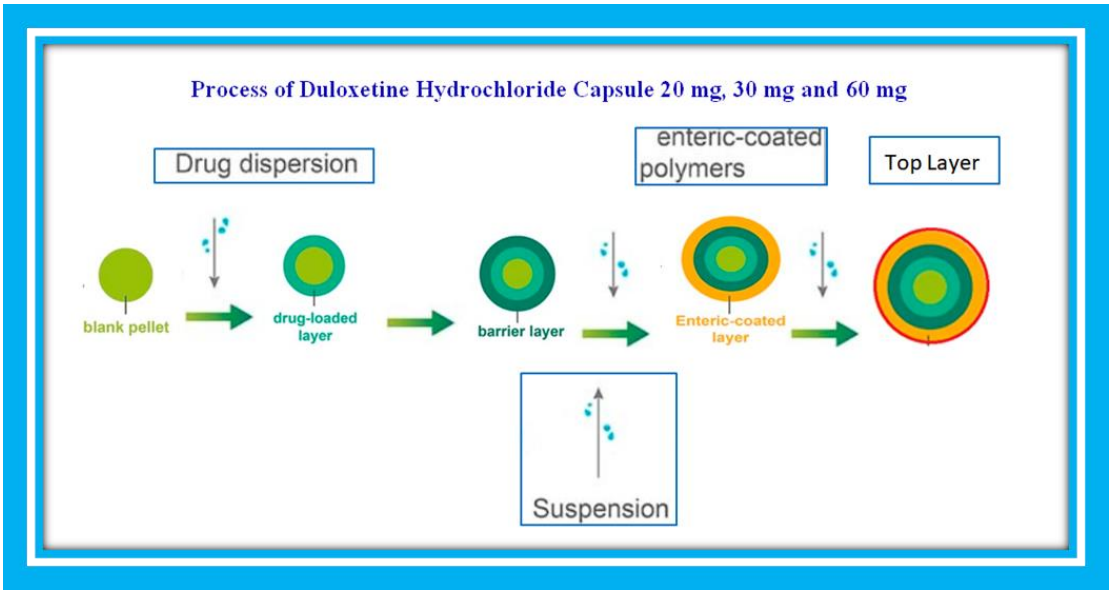

Fig 1: Development of Duloxetine Delayed Release Capsule

The process selection is Wurster based (Bottom spray) coating of the pellets.

It has the following stage as provided in the below diagram:

1. Drug Layer
2. Barrier Layer
3. Enteric Polymer Layer
4. Top Layer

The formulation development was initiated with the Wurster coating since RLD have used the Wurster coating to manufacture the Duloxetine Hydrochloride Delayed release capsule. The qualitative composition was kept similar to the Innovator. Control of particle size: Particle size distribution may affect drug layer coating. Therefore, appropriate particle size control at the final manufacturing step of the active substance should be established. The particle size selected was below 20 microns so that there is no issue of gun blockage during drug coating process. The excipients used for the delayed release capsule are commonly used for solid oral dosage forms: sugar sphere (base), hydroxy propyl methyl cellulose (binder), hydroxypropyl methylcellulose acetate succinate (enteric polymer), triethyl citrate (plasticizer), sucrose (Filler), Talc (antitacking agent), titanium dioxide (Opacifier), FD&C Blue No. 2 (Colour), gelatin (Capsule material), and sodium lauryl sulfate (Capsule material).

The formulation development of Duloxetine Hydrochloride Delayed release capsule was carried out based on the following five stages

Stage I: Formulation Development & Optimization in the Drug Layer

Drug Layer: Selection of Beads

Stage II: Formulation Development & Optimization of the Barrier/ Seal Layer:

Barrier Layer: Optimization of the sucrose in the barrier layer

Stage III: Formulation Development & Optimization of the Polymer Layer:

Polymer Layer: Optimization of Polymer Layer

Stage IV: Formulation Development & Optimization of the Top Layer:

Top Layer: Optimization of the Top Layer

Dissolution mapping of the final formulation with the final Innovator Bioequivalence Lot.

The final prototype was selected and multimedia dissolution was done in the following media.

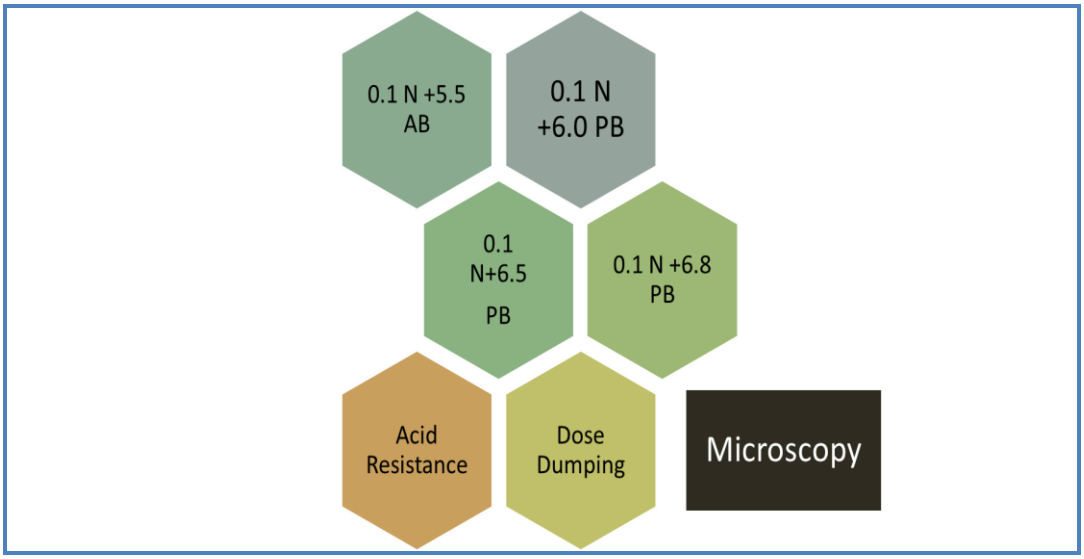

Fig. 2: Multimedia dissolution profile map of Duloxetine Hydrochloride.

Electron Microscope

The pellet cross section was done and the pellet diameter of Menovo pharmaceuticals was compared to that of the Innovator. The thickness of the each layer was calculated and tabulated for comparsion.

Ethanol Dose Dumping[4]

The innovator and Menovo formulation dose dumping in 40% ethanol was studied and evaluated.

Acid Resistance for 6 Hours

An acid resistance for 6 hour was done to check the integrity of the pellet in the acid media.

DISCUSSION & CONCLUSION

Formulation Development & Optimization in the Drug Layer

Drug Layer: Selection of Beads

A drug layering approach was selected using Wurster coating was selected over extrusion-spheronization because drug-layered beads typically have smoother surfaces and a narrower particle size distribution. These attributes are important for the subsequent delayed release bead coating. The drug substance was dissolved in purified water and sprayed onto the sugar bead using a bottom-spray fluid bed (Wurster) coating process to produce the drug-layered beads.[5] The drug substance had a low intrinsic binding property so the addition of a binder to the aqueous coating was considered necessary to maintain the physical integrity of the drug-layered bead during subsequent processing. The diameter of the final Delayed Release coated beads was proposed to be 700-1000 µm. In addition, beads less than 1 mm in size show a less significant food effect. A bead size of 500-600 µm was selected for drug layering. Sugar sphere are commercially available beads with a mean diameter of 500-600 µm were considered for evaluation. Sugar sphere was selected sine innovator have used sugar sphere. Duloxetine is BCS Class II drug (Low soluble drug), hence sugar sphere was selected due to good solubility. The high solubility of sugar beads combined with the low solubility of Duloxetine Hydrochloride, the drug substance, facilitates an efficient drug layering process. Commercially available sugar beads are provided with ≥ 85% of the beads meeting the particle size distribution (PSD) criterion of 500-600 µm[6]. Furthermore, batch-to-batch or vendor-to-vendor PSD variability for commercial sugar sphere beads was not found to be significant. The narrow PSD and sphericity enable a Wurster coating process to provide drug product with consistent content.

Physical parameters for commercially available Sugar beads with a 500-600 µm PSD are listed below: PSD: 250-350 µm with ≥ 85% of beads meeting criterion.[7]

- Loss on Drying (LOD): ≤ 7.0%
- Bulk density: ~ 0.80 ± 5% g/cc
- Sphericity degree: 0.90 ± 0.05
- Friability: < 0.1%
- Swelling index: ≤ 2 mL/g Prior to drug layering

Table 1: Dissolution for the selection of the quantity of the sugar sphere.

Batch Number	Details	2 Hour	5 min	10 min	15 min	30 min	45 min	60 min	75 min	90 min
		0.1 N HCl	pH 6.8 Phosphate Buffer							
D328286A	RLD	0	1	23	43	70	82	89	95	98
2DU2008001-4	Sugar sphere of 120.0 mg	1	7	20	39	70	83	90	95	98
2DU2101006-4	Sugar sphere of 80.9 mg	0	2	10	29	72	85	93	97	99
2DU2106011-4-4	Sugar sphere of 60.0 mg	0	2	11	40	76	89	95	97	98

Conclusion

From the above trial, we can observe that the dissolution in acid resistance is good in all the trials with different quantity of sugar sphere. However in the pH 6.8 phosphate buffer the dissolution differ till 15 minutes and from 30 minutes all the trials showed same dissolution. The sugar sphere of 80.9 mg was selected in between 120 mg and 60 mg since the batch with 120 mg resulted in greater capsule filled weight which ultimately resulted in pellets unable to fill in capsule size "1" while the sugar sphere with 60 mg resulted in processing difficulty since the base sugar sphere is too less to process the remaining manufacturing steps such as Barrier Layer, Polymer Layer and Top Layer. Therefore the sugar sphere 80.9 mg was selected in between the sugar sphere 120 mg and 60 mg as it comfortable pass the Q point of 75 % in 60 minutes.

Stage II: Formulation Development & Optimization of the Barrier/ Seal Layer

Barrier Layer: Optimization of the sucrose in the barrier layer

A barrier layer was applied using Wurster coating over the drug layer because drug-layered beads on contact with the polymer degrades and become unstable. The polymer consists of hydroxy propyl methyl acetyl succinate. This polymer on contact with the drug degrades instantly therefore to differentiate the polymer layer and the drug layer a sub coating seal layer is applied in between the two layers. The quantity of sucrose is an important critical material attribute in the barrier layer.

The functions of the separating layer, if required, are to provide a smooth base for the application of the enteric layer, to prolong the pellet's resistance to acid conditions, to improve stability by inhibiting any interaction between the drug and the enteric polymer in the enteric layer, and to improve stability by protecting the drug from light exposure. The smoothing function of the separating layer is purely mechanical, the objective of which is to improve the coverage of the enteric layer and to avoid thin spots in it, caused by bumps and irregularities on the core. It has been found that, when a pharmaceutically acceptable sugar is added to the separating layer, the pellet's resistance to acid conditions is markedly and surprisingly increased. Accordingly, such a sugar is included in the separating layer applied to the drug loaded beads of Duloxetine hydrochloride. A sugar-containing separating layer can reduce the quantity of enteric polymer required to obtain a given level of acid resistance. It therefore considerably reduces the expense of the present formulated product. Use of less enteric polymer reduces both the materials cost and processing time, and also reduces the amount of polymer available to react with duloxetine. The separating layer physically keeps the components in the core and enteric layers from coming into direct contact with each other. In some cases, the separating layer can also act as a diffusional barrier to migrating core or enteric layer components dissolved in product moisture. In the separate layer in addition to the above mentioned sucrose excipient such as finely powdered talc, is added as is convenient in the circumstances to fill and smooth the separating layer. The separating layer is applied by spraying aqueous solutions of the sugar in the preparation of a duloxetine layer. The smoothness and homogeneity of the separating layer can be improved, however, if the filler is thoroughly dispersed as a suspension in the solution of sugar and the suspension is sprayed on the core and dried, using equipment as described above in the preparation of cores with duloxetine layers. The difference in the sucrose quantity batch trials were taken and loaded in accelerated stability to see the influence of the quantity of sucrose in the barrier layer during 6 month stability.

Table 2: Accelerated Stability data of Duloxetine formulation with different % weight of barrier layer.

Batch Number Quantity of Sucrose/ capsule	Specification	2DU2012004-4 **14.00 mg/ capsule**	2DU2102007-4 **24.00 mg/ capsule**	2DU2106011-4-4 **36.20 mg/ capsule**
Condition	-	40°C/75%RH	40°C/75%RH	40°C/75%RH
Time Interval	-	**6 month**	**6 month**	**6 month**
Impurity D	NMT 0.2%	-	0.08	ND
Impurity C	NMT 0.2%	-	0.11	ND
Impurity H	NMT 0.2%	-	0.12	0.11

Maximum Unknown Impurity	NMT 0.2%	**3.21**	ND	ND
Total impurity	NMT 0.4%	**3.44**	**0.31**	**0.11**
0.1 N HCl				
120 minutes	NMT 10%	**6**	**6**	**3**
pH6.8 Phosphate Buffer				
5	-	11	22	13
10	-	26	36	23
15	-	46	51	42
30	-	72	74	73
45	-	83	86	86
60	NLT 80 %	89	92	93
90	-	92	94	97

Conclusion

From the above results, it can be seen that quantity of 36.2 mg of sucrose is required in the barrier layer to stabilize the formulation during the 6 months accelerated stability.

Table 3: The dissolution in different % weight of Barrier layer.

Batch Number	Details	0.1 N HCl	pH 6.8 Phosphate Buffer							
Time Interval		2 Hours	5 min	10 min	15 min	30 min	45 min	60 min	75 min	90 min
D328268A	RLD	0	1	23	**43**	70	82	89	95	98
2DU2112030-3C	18% seal layer	0	2	9	27	66	81	90	95	99
2DU2112032-3C	24% seal layer	0	2	11	33	72	86	93	97	98
2DU2112033-3C	28% seal layer	0	2	10	28	69	83	92	96	97
2DU2112034-3C	32% seal layer	0	12	29	69	84	92	96	98	99
2DU2106011-4-4	36% seal layer	0	2	11	**40**	76	89	95	97	98

Conclusion

From the above results, it can be seen that quantity of 36 % seal layer is required in the barrier layer to stabilize the formulation as well as match the dissolution.

Stage III: Formulation Development & Optimization of the Polymer Layer

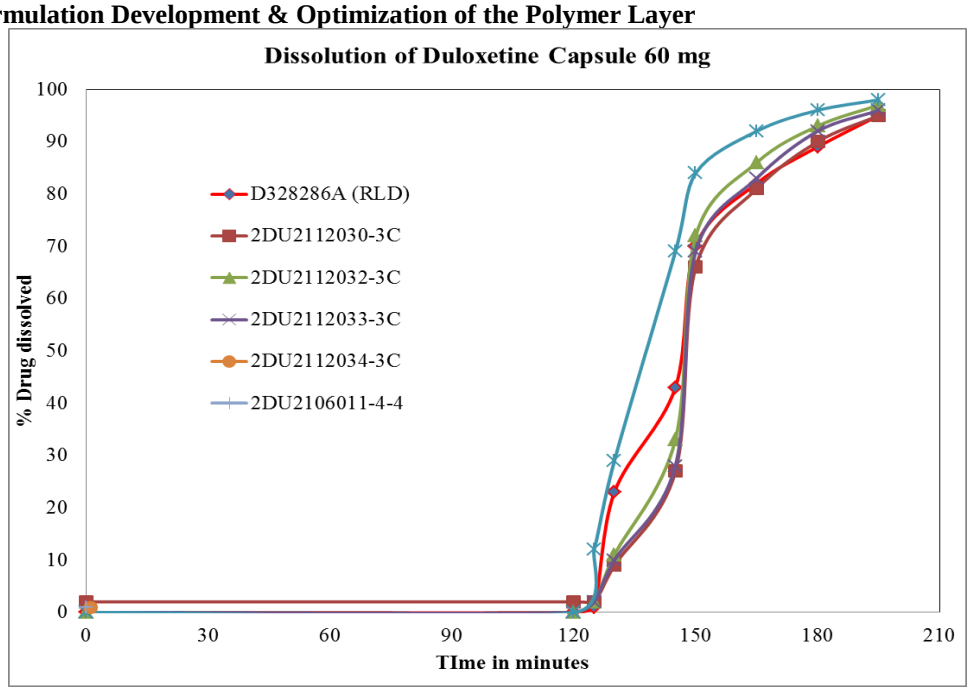

Figure 3: The dissolution in different % weight of Barrier layer.

Conclusion

Based on the above results, we can conclude that the 36 % weight gain matches in 15 minutes with the duloxetine innovator. The 15 minute time is critical with respect to the *in-vitro* and *in-vivo*. So we have finalized 36 % weight gain of barrier coating over the drug layer.

Stage III: Formulation Development & Optimization of the Polymer Layer

The delayed release Coated Beads are further coated with a delayed release controlling polymer to mimic the RLD release profile.[8,9]

The polymer Layer influence the: Dissolution as well as the Acid Resistance

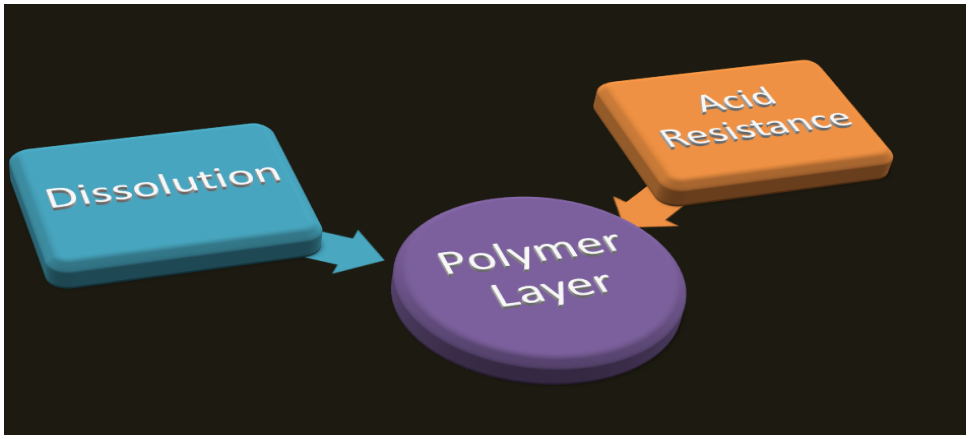

Figure 4: The Dissolution and Acid Resistance is affected by the Polymer layer coating.

Table 4: Acid Resistance with different % of Enteric Layer in the Duloxetine DR capsule.

0.1N HCl Acid Resistance at 100rpm, 1000ml							
Batch Number	Detail	**Time Point**					
		0.1 N HCl /Hours					
		2	**3**	**4**	**5**	**6**	**F2 - D328268A**
D328268A	RLD	0	0	24	63	78	N/A
2DU2201041-3B	41% polymer weight gain pellet inside capsule	0	4	44	72	81	**49**
2DU2201041-3C	44% polymer weight gain pellet inside capsule	0	2	30	66	78	**74**
2DU2201041-3D	47% polymer weight gain pellet inside capsule	0	1	15	50	69	**54**

Conclusion

It was observed that the acid resistance is similar to innovator in 44 % and better at 47% based on the similarity factor (***f2***). It was seen that at 41%, the Menovo formulation fails in the acid resistance. Due to constrain of capsule fill weight an enteric polymer layer of 44 % was selected for the duloxetine formulation.

Stage IV: Formulation Development & Optimization of the Top Layer

The top layer or the finishing layer is important for smooth capsule filling. This coating prevents static charge between the two pellets and facilitates for easy capsule filling. This layer consists mainly HPMC (Hydroxy propyl methyl cellulose) and is responsible for preventing the dose dumping in Ethanol at 40 % w/w.[10,11]

Table 5: The formulation with Top Layer Coating with different % of weight gain.

40% Ethanol and 60% 0.1N HCl Acid Resistance at 100rpm, 1000ml									
Batch Number	**Remark**	**40% Ethanol + 60% 0.1N HCl**							
		15	**30**	**45**	**60**	**75**	**90**	**105**	**120**
D328268A	Innovator	17	65	83	95	100	101	101	100
2DU2201041-3D	Without top layer	39	76	93	102	103	103	102	102
ZT0220101-4C-2	8 % Top layer	19	79	93	98	100	100	100	100
ZT0220101-4C-3	11 % Top layer	17	66	80	87	91	93	95	96
ZT0220101-4C-4	14 % Top layer	13	62	76	83	88	91	92	94
ZT0220101-4C-5	17 % Top layer	10	61	74	80	84	87	89	91

CONCLUSION

1. The dissolution in official media in 8% was not done since ethanol dose dumping is observed
2. The 11%, 14% and 17 % top-layer in the official dissolution media is presented below.

The innovator and the Menovo formulation were scanned under the microscope,[12,13] and the thickness of the innovator and our formulation is provided in the below figure and the table.

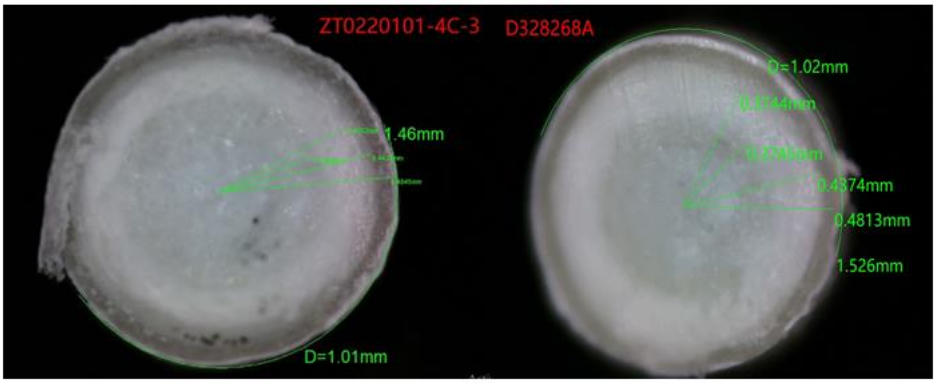

Figure 5: The Scanning electron microscope for the different thickness of the pellet.

Table 6: The comparsion of the thickness of the various layers in the pellet.

Details	Drug Layer	Barrier Layer	Polymer Layer	Top Layer
Innovator	100.0 µ	38 µ	43 µ	29 µ
Menovo	122.0 µ	35 µ	41 µ	20 µ

Acid Resistance for 6 Hour: As per US- FDA guideline

Table 7: Acid Resistance of Innovator and Menovo formulation

Time (minutes)	Innovator (N= 6 Capsules)	Menovo Formulation (N= 6 Capsules)
0.1 N HCl, 100 rpm, 1000 ml, 37 ±0.5 ^{0}C		
Batch Number :	**D328268A**	**ZW1220201**
Time in Hour	% Drug Released	% Drug Released
1 Hour	0	0
	% RSD- 67.6	*% RSD- 77.7*
2 Hour	0	0
	% RSD- 88.7	*% RSD- 26.2*
3 Hour	24	27
	% RSD- 6.1	*% RSD- 3.7*
4 Hour	63	61
	% RSD- 1.9	*% RSD- 0.9*
6 Hour	78	74
	% RSD- 1.4	*% RSD- 0.8*
Similarity Factor (F2)		**80**

Conclusion: From the above graph, it can be concluded that the Acid resistance of the Menovo is similar to the Innovator.

Alcohol Dose Dumping: 40 % Ethanol and 60 % 0.1 N HCl for 2 hours

Table 8: Ethanol dose dumping at 40 % Ethanol

Time (minutes)	Innovator (N= 6 Capsules)	Menovo Formulation (N= 6 Capsules)
40 % Ethanol+ 60 % 0.1 N HCl ; 1000 ml, 100 rpm, 37 ±0.5 ^{0} C		
Batch Number :	**D328268A**	**ZW1220201**
Time in minute	% Drug Released	% Drug Released
15 minute	17	17
	% RSD- 16.0	*% RSD- 34.5*
30 minute	65	66
	% RSD- 10.0	*% RSD- 12.0*
45 minute	83	80
	% RSD- 8.8	*% RSD- 10.0*
60 minute	95	87
	% RSD- 5.9	*% RSD- 8.4*

75 minute	100	91
	% RSD- 4.0	*% RSD- 6.2*
90 minute	101	93
	% RSD- 3.1	*% RSD- 4.5*
105 minute	101	95
	% RSD- 2.6	*% RSD- 3.4*
120 minute	100	96
	% RSD- 2.3	*% RSD- 2.7*
Similarity Factor (F2)		**62**

Conclusion: From the above graph, it can be concluded that the Ethanol Dose dumping of the Menovo is similar to the Innovator.

Scale-up Principles for Bottom Spray Fluid Bed Coating

Process variables most likely to impact the quality of coated beads were optimized at the production commercial batch scale. A batch at commercial scale was used to confirm the critical process parameter ranges and consistent product performance for the drug layering, barrier layer, Delayed release polymer coating and finally Top layer coating unit operations. The commercial batch was processed in a Tofflon-HO (DGC 800) with a 9 column Wurster HS insert. The Wurster machine has nine partition columns and nine spray nozzles. [14] The below figure illustrates the key operational features of this equipment, specifically the nine partition columns and spray nozzles. Each of these nine configurations has the same geometry and dimensions as the single-spray unit.

Figure 6: Fluid Bed Processor and Partition Columns.

- The length of the Fluid Bed processor in commercial plant is: 3500 centimeter
- The width of the Fluid Bed processor in commercial plant is: 2200 centimeter

The Occupancy of this machine is 80-550 Kg. The distance between the bottom of the draft tube and the air distribution plate is 43 mm.

The gun nozzle used during the process is 1.8 mm

Figure 7: Nozzle Gun and Filer Bag

The filter bag used in the machine is 5 micron during the drug layer process since the drug is below 20 micron and in the subsequent manufacturing step such as Barrier Layer, Polymer and Top layer the filter bag used in the machine is 145 micron.

Bioequivalence Study of Menovo Formulation

The bioequivalence study was done with Healthy Chinese subjects for both fasting and fed state.[15] The numbers of subjects enrolled were 48 for fasting study while 28 for fed study. The results for both fasting and fed showed bioequivalence. There were 7 withdrawn due to vomiting and adverse events and finally 41 subjects completed the study. The bioequivalence for the fasting is provided below.

Table 9: Bioequivalence study of Menovo formulation with Innovator in fasting condition.

Pharmacokinetic Parameter	Number of Subjects	Ratio %	90% CI	Power	CV
C_{max}	41	91.91	85.62-98.67	94.3	18.29
AUC_{0-t}	41	95.54	90.84-100.49	>99.9	12.92
$AUC_{0-infinity}$	41	95.43	90.76-100.33	>99.9	12.82

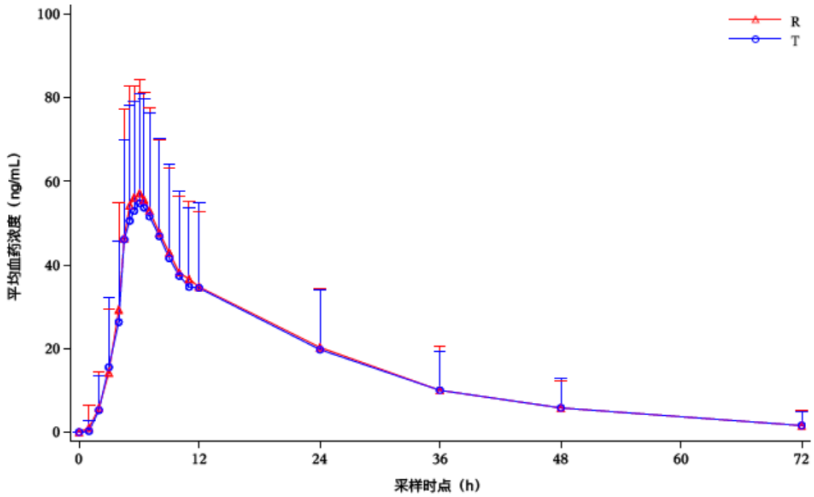

Figure 8: Bioequivalence study of Menovo formulation with Innovator in fasting condition.

The bioequivalence study was done with Healthy Chinese subjects fed state. The numbers of subjects enrolled were 28 for fed study. The results for both fasting and fed showed bioequivalence. There were 3

withdrawn due to vomiting and adverse events and finally 25 subjects completed the study. The bioequivalence for the fed study is provided below.

Table 10: Bioequivalence study of Menovo formulation with Innovator in fed state

Pharmacokinetic Parameter	Number of Subjects	Ratio %	90% CI	Power	CV
C_{max}	25	96.40	89.04-104.36	98.8	15.78
AUC_{0-t}	25	98.42	93.74-103.33	>99.9	9.62
$AUC_{0-infinity}$	25	98.50	93.95-103.27	>99.9	9.33

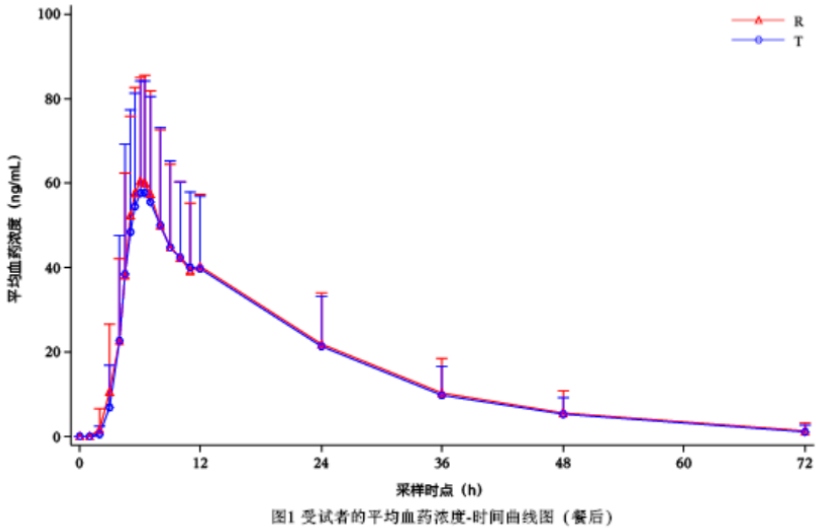

Figure 9: Bioequivalence study of Menovo formulation with Innovator in fed condition.

CONCLUSION

The bioequivalence of the Duloxetine delayed release capsule 60 mg was successful along with accelerated stability data for 6 months. The formulation showed superior results compared to the innovator in 5%, 20% and 40% ethanol dose dumping. The formulation also showed superior acid resistance for 6 hours. The formulation development of duloxetine delayed release capsule was based on the Wurster coating using MUPS technology platform. The formulation was scalable from the research lab to the commercial production plant.

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