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Research Article

Development of Mebeverine HCl Prolonged-Release Mini-Tablets by Thermoplastic Granulation Technique

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ABSTRACT

Mebeverine HCl (MH) is a biopharmaceutics classification system (BCS) class-I drug, and thus, it possesses high solubility in aqueous media across the biological pH range. The marketed reference product is a multi-unit particulate system (MUPS) containing prolonged-release pellets filled in hard gelatin capsules. In the conventional manufacturing process, a huge quantity of solvents (aqueous and/or organic) is used to manufacture such a dosage form. Additionally, it demands more processing time and effort. Therefore, a prolonged-release capsules dosage form of MH was formulated using a thermoplastic (melt) granulation technique without the usage of any solvent. Prolonged-release mini-tablets sized 2 mm in diameter were developed as per quality by design principles. A 2^3 full-factorial design of experiment was applied to optimize levels of drug release controlling ingredients that include a hydrophobic meltable binder (hydrogenated castor oil) cum matrixing agent, a hydrophilic meltable binder (polyethylene glycol), which may act as pore former also, and a release-controlling polymer (ethylcellulose). The optimized formulation was found stable. Dissolution profiles of the optimized formulation were found similar to the marketed reference product in different media across the physiological pH range. In conclusion, the explored solventless process was capable of manufacturing the MUPS dosage form of MH prolonged-release capsules, which is stable and pharmaceutically equivalent with the reference product. The developed process is more beneficial to small and medium scale industries, as it does not require any special and costly equipment, significantly decreases the manufacturing cost, and increases productivity compared to the conventional processes, which is mentioned in literature.

Introduction

It is well established that pellets as a form of MUPS are versatile drug delivery system, as it provides diversified applications varying from improved aesthetic look to control the drug release and prevent chemical incompatibilities. Hence, the market growth of such dosage forms is exponential. Current techniques used to prepare this dosage form are extrusion, fluid bed granulation, layering over the inert core, spray drying, spray congealing, etc. However, high manufacturing cost and capital expenditure on equipment restrain the small and medium scale enterprises (SMEs) from participating in this growing market.[1-3]

MH is categorized in BCS class-I, and thus, it possesses high solubility in the aqueous media across the biological pH range. A prolonged-release formulation is available in the market, which is a MUPS containing prolonged-release pellets filled in hard gelatin capsules.[4] In the conventional manufacturing process of a MUPS, a huge quantity of solvents (aqueous and/or organic) is used. Additionally, it demands more processing time and effort. Further, manufacturing of the pellets requires specialized equipment, like extruder, spheronizer, Wurster processor, etc., and the skilled workforce to operate such manufacturing processes.[5,6] So, it is difficult to adopt such a process for SMEs due to huge capital expenditure in the conventional manufacturing process to prepare such dosage forms. So, here an attempt has been made to formulate prolonged-release mini-tablets by thermoplastic granulation technique using

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conventional equipment and without the usage of any solvent.

Thermoplastic (melt) granulation is an emerging technique, which encompasses the benefits of both dry and wet granulation methods. It embodies an innovative granulation technique capable of mixing and agglomerating pharmaceutical powders to produce uniform granules suitable for the manufacturing of pharmaceutically elegant solid dosage forms. Thermoplastic granulation offers several advantages, like the absence of solvent, a suitable process for granulation of moisture sensitive drugs, reduced processing time, ability to granulate powders with poor flow, and poor compressibility.[7-9]

Many prior arts were referred to have insight on excipients and process, parameters studied for the melt granulation process and their impact on the finished dosage form. Prior art for formulation of the controlled release beads coated with hydrogenated castor oil (HCO) by tumbling melt granulation (TMG) is reported. In this study, core drug-containing beads were pre-heated in centrifugal fluidized granulator (CF) at 61 to 63°C. HCO was gradually fed on the pre-heated beads, which were subsequently cooled to room temperature to yield the controlled release beads of four different drugs with different solubility, namely, nicotinamide, isoniazid, theophylline, and salicylic acid.[10]

In another prior art, the melt granulation technique was evaluated to improve the dissolution properties of a poorly water-soluble drug, griseofulvin. Granules were prepared by melt granulation of the drug with hydrophilic meltable binders and other excipients in a lab-scale high shear mixer. After the characterization of the formulated preparation, it was concluded that the dissolution rate of poorly water-soluble drugs can be enhanced by the melt granulation technique.[11]

In a study, solid dispersions of cefpodoxime proxetil, a BCS class-IV drug with water-soluble carriers, like PEG 4000 and PEG 6000, were successfully prepared by using hot melt granulation and solvent evaporation techniques to enhance the solubility of the poorly soluble drug.[12]

In an investigation, various lipid-based materials were investigated to controlled release matrix tablets of the hydrophobic drug. The tablets were prepared by direct compression process using compritol, precirol, glyceryl monostearate, cetostearyl alcohol, and eudragit as release controlling agents in different prototypes. It was found that friability was decreased, and tablet tensile strength was increased significantly with an increase in the amount of hydrophobic materials. At the higher hydrophobic level (50% of the matrix), the rate, and extent of drug release were significantly reduced.[13]

Extended-release matrix tablets of tramadol HCl were successfully prepared using a combination of hydrophilic and hydrophobic polymer consisting of ethylcellulose, hydroxypropyl methylcellulose (HPMC) K15M, carbopol, and xanthan gum in an optimized ratio.[14]

In a study, melt granulation in a high shear mixer was evaluated as an alternative to conventional wet granulation method using theophylline as a model drug. Here, a combination of the mixture and factorial designs of experiments were employed to study the effects of process parameters, *viz.*, impeller speed and massing time, and excipients mixture formulae on size of the granules. By using the response surface method, excipients mixture formula and the studied process parameters were successfully optimized.[15]

In the present work, extended-release mini-tablets of mebeverine HCl, a highly soluble drug was prepared using a solventless melt granulation technique by selecting suitable excipients and optimizing their level in the formula. Here, levels of a hydrophilic meltable binder, polyethylene glycol, a hydrophobic meltable matrixing agent, hydrogenated castor oil, and a drug release controlling polymer, ethylcellulose were optimized to prepare extended release mini-tablets. Outcome of the work has the potential to enable the SMEs by providing a cost-effective way for manufacturing of MUPS dosage form of MH using a conventional set of equipment.

Materials and Methods

Materials

All the raw materials namely MH (Piramal Healthcare), microcrystalline cellulose-avicel PH 102 (FMC), ethylcellulose 10 cps (Ashland), hydrogenated castor oil (BASF), polyethylene glycol (Clariant), and magnesium stearate (Peter Graven) were provided by Piramal Enterprises Ltd., Pharmaceutical Development Services, Ahmedabad, India. All other reagents used were of analytical grade.

Characterization Methods

Assay

Solvent preparation: Solvent or diluents was prepared by adding 5 mL of triethylamine to 1,000 mL of distilled water, and later pH was adjusted to 3 using 30% v/v of ortho-phosphoric acid in water.

Sample preparation: Ten capsules were weighed, and the average weight was calculated. The content of capsules was crushed into a fine powder. The resultant powder equivalent to 200 mg of MH was transferred separately to 100 mL volumetric flask containing the diluents, and it was stirred for 10 minutes. The volume was made up to the mark with the diluent. The solution filtered through a 0.45 µ nylon membrane filter. Finally, the above stock solution was diluted using diluents to prepare a sample solution of 20 µg/mL, and then, absorbance of the sample solution was taken using a UV spectrophotometer at 263 nm, and the concentration of the MH was calculated by linearity equation of the calibration curve.[16]

Dissolution: Following dissolution method was used to generate dissolution profiles.[17]

Apparatus: USP-I (basket)
Agitation speed: 100 RPM
Temperature: 37 ± 2°C
Media: pH 6.8 phosphate buffer for prototype development
Additionally, pH 4.5 acetate buffer and 0.1 N HCl (pH 1.2) for final optimized batches
Media volume: 900 mL
No. of units: 6

Stability: The optimized formulation was packed in 40 cc, round, white HDPE bottle with a child-resistant cap. Thirty capsules were packed in each bottle, and the samples were stored in 40 ± 2°C/ 75 ± 5% RH (accelerated condition) as recommended by ICH Q1A (R2) guidance.[18]

Experimentation: Following drug release controlling excipients were selected based on their functionality and suitability for the melt granulation technique.

- Ethylcellulose (EC) - A drug release controlling polymer-melting point: ~160°C
- Hydrogenated castor oil (HCO) - A hydrophobic meltable binder that may form an insoluble matrix with EC. It may work as a plasticizer also for ethylcellulose - melting point: 62 to 86°C
- Polyethylene glycol 6000 (PEG 6000) – A hydrophilic meltable binder, which may act channeling agent in the matrix; melting point: 49 to 63°C

In addition to drug release controlling ingredients, some non-drug release controlling ingredients were selected, such as, filler, lubricant, and capsule shells. Being a modified release dosage form, an insoluble diluent is preferable. So, microcrystalline cellulose, commonly used filler in the pharmaceutical industry was selected. Lubricant is required for easy ejection of compressed mini-tablets from the die, and to avoid sticking defect. So, magnesium stearate, a widely used lubricant was selected.

Levels of drug release controlling excipients, EC, HCO, and PEG 6000 were optimized using a 2^3 full factorial design of experiments (DoE) with three center points. Targets for dissolution profiles were decided based on the dissolution profile of marketed reference products. Detail of factors, levels, and responses are tabulated in Table 1. Formulae of DoE trials are given in Table 2. The process was followed, as mentioned in Fig. 1 in all the experimental runs.

Results

Dissolution results for all three responses of DoE trials are tabulated in Table 3.

Response 1–Dissolution at 1-Hour

As illustrated in Fig. 2, the Pareto chart shows that EC has a negative effect, and PEG have a positive effect on dissolution at 1-hour, which means that the drug release decreases with an increased level of EC, while it increases with an increase in PEG level. It can be observed in the 3D surface plot also. The other model terms did not show any significant effect on drug release at 1-hour. The interaction plot reveals that there is no interaction between significant model terms.

Response 2–Dissolution at 4 Hours

In Fig. 3, the Pareto chart shows that factor A-EC and B-HCO have negative effects while factor AB (EC and HCO) have a positive effect on the response. The other model terms did not show any significant effect on the response. The interaction plot reveals that there is no interaction between significant model terms. The 3D surface plot reveals that dissolution at 4 hours decreases with an

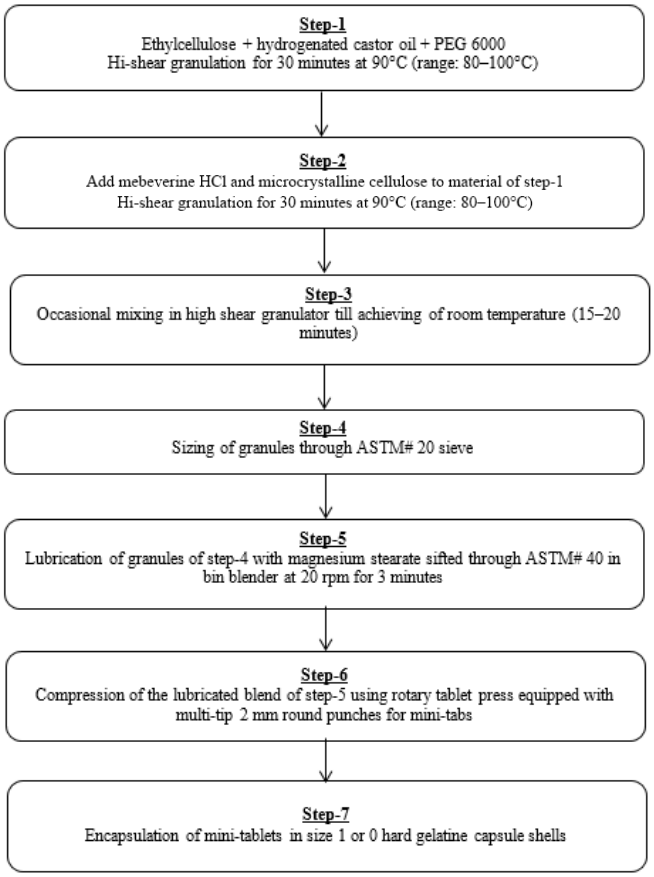

Fig. 1: Manufacturing process flow for DoE trial batches

Table 1: Factors, levels, and responses for a 2^3 full factorial experimental design

Factor	*-1 level (mg)*	*+1 level (mg)*	*Response [target]*
A: Ethylcellulose 10 cps	20	100	D(1): Dissolution at 1 hr [NMT 30%]
B: Hydrogenated castor oil	20	100	D(4): Dissolution at 4 hr [between 45% to 65%]
C: Polyethylene glycol	2	10	D(12): Dissolution at 12 hr [NLT 80%]

Table 2: Formula of experimental runs

Batch Size: 300 g												
Batch#		*M1*	*M2*	*M3*	*M4*	*M5*	*M6*	*M7*	*M8*	*M9*	*M10*	*M11*
Ingredient	*Category*	*Qty/unit (mg)*										
Mebeverine hydrochloride	Drug substance	200	200	200	200	200	200	200	200	200	200	200
Microcrystalline cellulose AVICEL® PH 102	filler	10	10	10	10	10	10	10	10	10	10	10
Ethylcellulose 10 cps	Drug Release controlling polymer	100	60	100	100	20	60	20	60	100	20	20
Hydrogenated castor oil	Hydrophobic meltable binder	20	60	20	100	100	60	20	60	100	100	20
Polyethyleneglycol (polyglykol 6000 P)	Hydrophilic polymer	2	6	10	10	2	6	10	6	2	10	2
Magnesium stearate	Lubricant	5	5	5	5	5.	5.	5	5	5	5	5
Total (target weight)		337	341	345	425	337	341	265	341	417	345	257
No. of minitablets per capsule		48	49	49	61	48	49	38	49	60	49	37
IPQC parameters												
Average weight of minitablets per station (7 minitablets)		49 ± 2.45 mg (±5%)			Hardness			20–30N				

Table 3: Responses of DoE study: dissolution profiles

	Factor 1	*Factor 2*	*Factor 3*	*Response 1*	*Response 2*	*Response 3*
Run	*A: EC (mg)*	*B: HCO (mg)*	*C: PEG (mg)*	*D (1 hr) (%)*	*D (4 hr) (%)*	*D (12 hr) (%)*
M1	100	20	2	8	33	68
M2	60	60	6	20	52	81
M3	100	20	10	17	36	75
M4	100	100	10	14	27	53
M5	20	100	2	38	58	90
M6	60	60	6	24	55	78
M7	20	20	10	76	99	99
M8	60	60	6	22	50	78
M9	100	100	2	9	20	59
M10	20	100	10	75	65	89
M11	20	20	2	71	99	99

increase in the EC level. Dissolution at 4 hours remains fairly constant with an increase in HCO at higher levels of EC, while it decreases with an increase in HCO level at lower levels of EC.

Response 3–Dissolution at 12 Hours

As illustrated in Fig. 4, the Pareto chart shows that factor A-EC and B-HCO have negative effects on the response. The other model terms did not show any significant effect on the response. The interaction plot shows that there is no interaction between significant model terms. The 3D surface plot reveals that dissolution at 12 hours decreases with an increase in the level of EC and HCO.

Optimized Trial

Based on the outcome and recommendation from DoE trials, an optimized batch was manufactured. The formula of the optimized trial batch is tabulated in Table 4.

Capsules filled with mini-tablets were tested for dissolution in the media to cover physiological pH range, i.e., 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer. As shown in Fig. 5, the dissolution profile of the optimized batch (M12) is comparable with

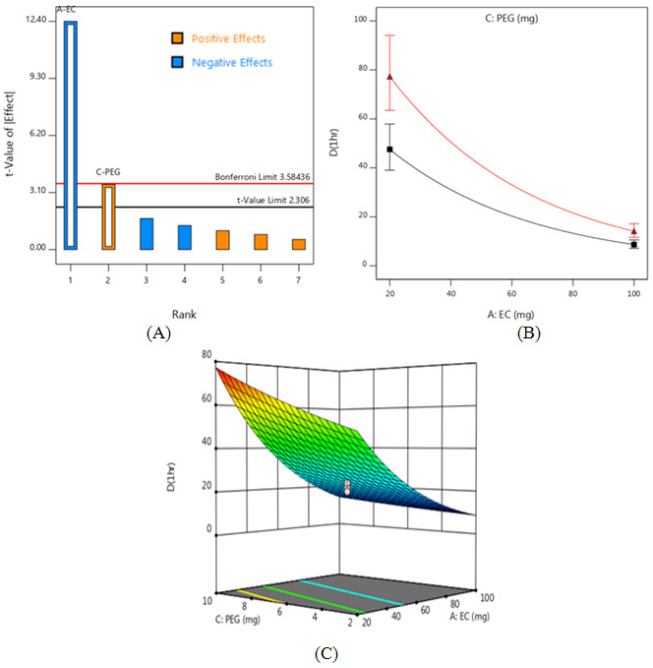

Fig. 2: Model graph for response 1: **(A)** Pareto chart; **(B)** Interaction plot; **(C)** 3D surface plot

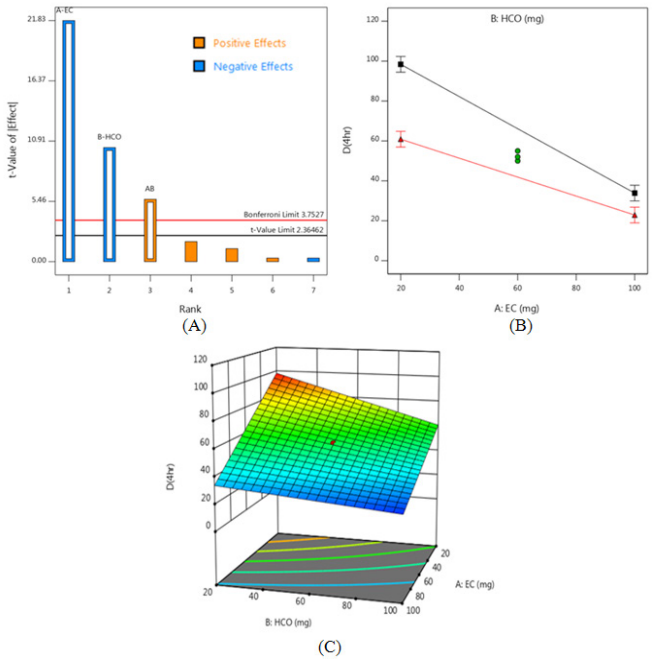

Fig. 3: Model graph for response 2: **(A)** Pareto chart; **(B)** Interaction plot; **(C)** 3D surface plot

that of the reference product in all the tested dissolution media.

Alcohol-Induced Dose-Dumping Study

Co-administration of alcoholic beverages may affect drug release from a modified release solid oral dosage form leading to rapid dumping of complete or fraction dose. Dose-dumping can pose a significant risk to patients, either due to safety issues or diminished efficacy or

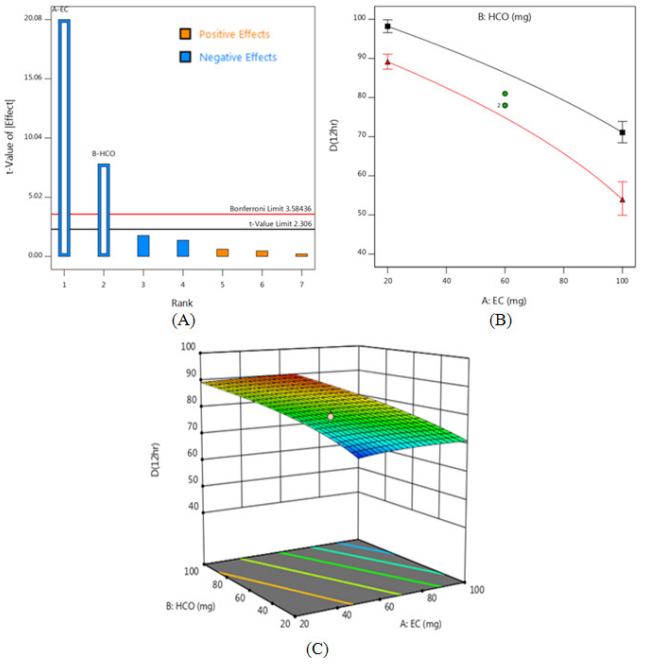

Fig. 4: Model graph for response 3: **(A)** Pareto chart; **(B)** Interaction plot; **(C)** 3D surface plot

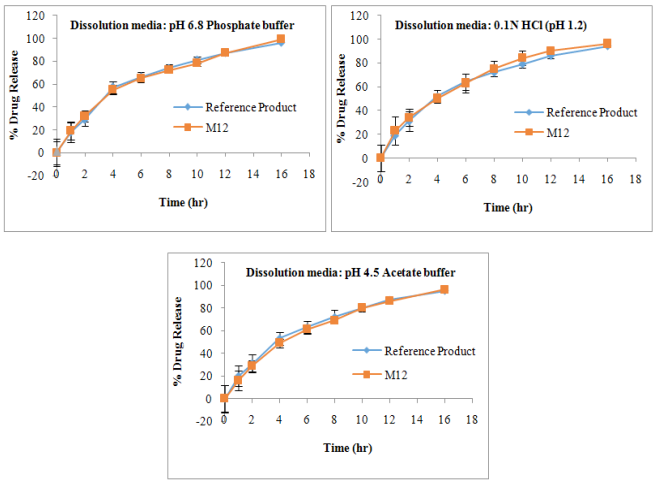

Fig. 5: Comparative dissolution profile of optimized trial and marketed reference product in different pH dissolution media

both.[19,20] Therefore, a dissolution study was carried out on the optimized batch (batch# M12) as per the US-FDA recommendation. Dissolution profiles of the optimized batch (M12) were comparable without (0% v/v) alcohol and 40% v/v alcohol in pH 0.1 N HCl, as shown in Fig. 6.

Stability Study

Stability data tabulated in Table 5 reveals that the hardness of mini-tablets, assay, and drug release profiles are comparable at initial and after 6-month exposure to accelerated condition (40 ± 2°C/ 75 ± 5% RH).

Hence, it can be concluded that the explored manufacturing process and the optimized formula are

Table 4: Formula for optimization and reproducibility trials

Batch#	*M12*	
Ingredient	*Qty/capsule (mg)*	*% w/w*
Mebeverine hydrochloride	200	63.09
Microcrystalline cellulose AVICEL® PH 102	10	3.15
Ethylcellulose 10 cps	64	20.19
Hydrogenated castor oil	34	10.73
Polyethyleneglycol (Polyglykol 6000 P)	4	1.26
Magnesium stearate	5	1.58
Total weight of content	317	100
No. of minitablets of 7 mg weight	45 no.	-
Size 1, hard gelatin capsule shell	76	-
Total weight of capsule	393	-

Table 5: Stability study data

Batch# M12
Pack style: 40 CC, round, HDPE bottle with CR cap, 30 counts
Stability condition: 40 ± 2°C/ 75 ± 5% RH (accelerated)

Test	*Target specification*	*Initial*	*Accelerated condition, 6 months*
Mini-tablet hardness	20–30 N (average of 20 units)	25.6 N	24.2 N
Assay (%)	95–105	98.8	100.2
Dissolution [pH 6.8 phosphate buffer, 900 mL, apparatus: USP-1 (basket), 100 rpm, N = 6]			
1-hour	Not more than 30%	19%	21%
4 hours	Between 45 and 65%	55%	52%
12 hours	Not less than 80%	89%	88%

capable to produce a stable prolonged-release MUPS dosage form of mebeverine HCl.

Discussion

The optimized formulation was found satisfactory in all the pharmacotechnical parameters, like processability, drug-release profile, alcohol-induced dose dumping, and stability. Hence, it can be concluded that the design space predicted by the selected statistical design was appropriate. Further, the developed process does not use any solvent, there is no need of drying unit operation, and thereby the overall processing time is reduced. Conventional equipment, *viz.*, vibro-sifter, rapid mixer granulator, and tablet compression machine were used in the manufacturing process. Hence, it was concluded that the demonstrated solventless melt granulation process is capable to prepare a stable prolonged-release MUPS capsules of mebeverine HCl. Comparison of the demonstrated melt granulation process and conventional (extrusion-spheronization and Wurster) process, which is commonly used to prepare MH 200 mg prolonged-release capsules, are tabulated in Table 6.

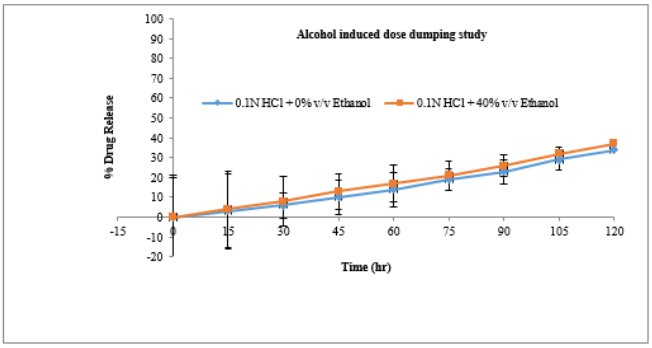

Fig. 6: Comparative dissolution profile of optimized trial in without alcohol and 40% v/v alcohol-containing dissolution media

Table 6: Advantages of the demonstrated melt granulation process over the conventions process

Demonstrated melt granulation	*Conventional process[21]*
Requires no special equipment	Requires special equipment like rotary fluid bed dryer or extruder–spheronizer
Solventless process	Using huge amount of solvent As mentioned in cited patent following amount of solvent is required to prepare a batch of 4,000 capsules: Core: 700 mL dispersion–7 min Drying time: ~1-hr Coating: 150 g weight gain–20% dispersion which contains–600 g water–150 min
Less no. of unit operation: Dispensing, sifting, granulation, lubrication, compression, encapsulation	More no. of unit operations: Dispensing, sifting, dry-mixing, granulation, extrusion, spheronization, drying, sifting, coating, encapsulation
Requires less processing time and energy	Requires more processing time and energy

It is evident that the demonstrated melt granulation technique is more productive, cost-effective, and does not require any specialized equipment and so, it may potentially enable the small and medium-scaled pharmaceutical industries to participate in the growing market of MUPS dosage forms.

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