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Formulation development of directly compressible mebevarine tablets using superdisintegrant: A way to investigate quality atributes, *in vitro* release kinetics and stability profile

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Abstract: In order for preparing a solid oral dosage form, tablet quality is of significant concern. Compressibility behavior of different powders and mixtures of formulations and release pattern of any tablets are characteristic measures to define prerequisite quality attributes of any compressed formulations. There are basically two major methods that can be adopted for the preparation of tablets including granulation and direct compression. Later process offer fewer processing steps and agreeable release profile with acceptable quality parameters and hence preferred over granulation method. In this investigation Mebeverine hydrochloride an anti-muscarinic drug is studied for compression and release behavior using various concentrations of filler binders and disintegrants via rotatable central composite design (CCRD) option of design expert (software). Nine formulations were developed from F1 to F9 with Crospovidone (superdisintegrant) as (X_1) (-α=1.17% to ±α=6.83%) and microcrystalline cellulose (Avicel 102, Filler/binder) as X_2 (-α = 29.82% to ± α = 65.18%). Disintegration Time (DT) as (R_1) and Hardness in (kg) as (R_2) were determined as two dependent response variables. The performance of powder blends and formulations was analyzed by micromeritic and physico-chemical and assessments. Dissolution comparisons were statistically analyzed by ANOVA and model dependent and in-dependent methods. Best fit model was found to be Hixon-crowell's model (r^2 = 0.995) followed by Weibull's model (r^2 = 0.985). The Trial formulations F2, F4, F6 and F8 were also studied on accelerated conditions (40±5ºC 75%±5% RH) for stability tests and validity of the formulations in months were also determined between 35-39 months.

Keywords: Super disintegrant, mebeverine, direct compression, release behavior, design expert, Hixon crowel.

INTRODUCTION

Tablet manufacturing is a complex multi-stage process where ingredients in each process change their original physical state (Grymonpre *et al*., 2017). Powder compaction is a significant process in pharmaceutical material processing. The forecast of basic and mechanical properties of tablets dependent on raw ingredient properties and procedure parameters is as yet troublesome or rather unimaginable, despite the fact that the powder compaction process was the object of various logical examinations over the decade. The principle purpose behind the fragmented consistency is absolutely the still constrained procedure understanding because of the multifaceted nature of the powder compaction process (Isabell *et al*., 2019). "Optimization" is a technique for developing a distinctive composite product within determined condition thence estimated by different tests, result obtained by them a term optimized formulation is determined as optimal (Hafeez *et al*., 2019). Direct compression is a well-liked process as it is the shortest, simplest and least complicated method for tab letting. But to ensure consistency and homogeneity for low quantities of actives and compressibility and flow irregularities in case of larger volumes of API poses great difficulties to formulation scientist (Maltais *et al*., 2015). Optimization of formulation with Experimental Design offers reduces costs, but main challenge in formulation design is to use as main excipients the ones that have the best compressibility properties including Avicel, Microcelac (or Cellactose), Coprocessed mixes such as *Prosolv Easy Tab SP* to resolve the compressibility issues. In case of lack of success in the Direct Compression process, wet granulation may be tried with stronger binders as methylcellulose (Methocel A) or hydroxipropyl cellulose (Klucel), low viscosity grades and or use direct compression excipients) (Prakash *et al*., 2019; Moshiur *et al*., 2017; Muzikova *et al*., 2015). If the powder is fine, the poor flow properties and the expansion of the entrapped air after compression could be another reason of the low tablet hardness. Improvement of the flow properties with better flowing silicified microcrystalline cellulose (Prosolv SMCC 90) and decreasing the speed of compression to let enough time for bond consolidation may have positive effect (Deeb *et al*., 2019). On the other hand in several cases, the disintegration time of solid

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dosage forms is long enough to produce suitable therapeutic response. Mechanism of disintegrations includes deformation recovery, swelling, wicking, and particle repulsion (Bolhuis *et al*., 2015). To facilitate disintegration and drug release behavior different modified materials are introduced and tested as release modifiers (Dilebo & Gabriel 2019). This study has chosen Mebeverine Hydrochloride (MebHCl) as a model compound. It is a musculotropic antispasmodic i.e cholinergic muscarinic antagonist & belongs to Bio-Pharmaceutical classification II (BCS-II) with highly permeability and low solubility profile (Grymonpré *et al*., 2017). It is indicated for irritable bowel syndrome (IBS) and polymicrobial complications (Druginfosys, 2015).

The main aim of this research was to formulate instant release tablets with various forms of direct compression excipients, comparison of their compressibility, dissolution and disintegration profiles. Mebeverine was used as a standard for immediate release tablets. It is required to find an effective disintegrant with very good disintegrating and compactability qualities. Furthermore, study focuses on establishing various powders combinations and to study the impact of their properties on the tablet formulation and dissolution rate.

MATERIALS AND METHODS

Mebeverine HCl was provided by Nabiqasim Pharma (Pvt.) Limited as gift sample. Crospovidone (FMC Bio-polymer, Philadelphia, USA), Avicel (Micro-crystalline cellulose), (BASF, Ludwigshafen, Germany), Methanol and Potassium dihydrogen phosphate (Merck, Darmstadt, Germany), Aspartame (Lubon Industry Company Limited, China), Sodium hydroxide (Merck, Darmstadt, Germany)

Equipments and apparatus

Analytical Balance (AUW-220, UNI Blog, Schimadzu Corporation, Japan), Single Punch Compression Machine (TDP-1.5), pH Meter (PCSIR Laboratories, Karachi, Pakistan), Hardness Tester (Seisakusho, Fujiwara, Ogawa Seiki Company Limited, Kyoto, Japan), Friabilator (Curio FB 2020, Pakistan), USP Basket-Rack Assembly (DA 6D, Veego, India), USP Dissolution Apparatus II (DA 6D, Veego, India), Sieve (710 µm mesh aperture), UV Spectrophotometer (UV-1800 Schimadzu Corporation, Kyoto, Japan), Sonicator (LC60H, Elma, Germany), Climatic Chamber (BC 0786, Abrowill, Canada)

Mebeverine hydrochloride tablets optimization via central composite rotatable design (CCRD)

Response surface methodology (RSM) was used for optimizing and developing the formulations by software Design Expert® (version 7.0, Stat-Ease Inc.,). Formulations were designed (F1, F2, F3, F4, F5, F6, F7, F8 and F9) used random central composite rotatable design (CCRD) (Bushra *et al*., 2014) in such a way that few formulations were on factorial (F1, F2, F3 & F4) and axial points (F5, F6, F7 & F8) with one centre point (F9) used two independent variables, i.e. Crospovidone (1.17-6.83) (X_1) as super-disintegrants and Avicel (Microcrystalline cellulose) (29.82-65.18) (X_2) as binder with five different levels, used two dependent responses Disintegration time (R_1) and Hardness (R_2). The considered two variables equation for response model is as equation 1;

$$y = (b + x) + \sum_{i=1}^{3} b_1 x_1 + \sum_{i=1}^{3} b_1 x_1^2 + \sum_{i=1}^{3} \sum_{i=i+1}^{3} b_1 |x||x| \quad (1)$$

Evaluation of powder blends

Blends of powder were evaluated by Carr's Index Eq.2, Hausner's ratio Eq. 3 and Angle of repose Eq. 6, using following equations:

$$Carr's\ Index = 100 \times \left(\frac{Tapped\ bulk\ density - Poured\ bulk\ density}{Tapped\ bulk\ density}\right) \quad (2)$$

$$Hausner's\ ratio = \frac{tapped\ density}{bulk\ density} \quad (3)$$

$$Poured\ Bulk\ Density = mass\ of\ powder/bulk\ volume \quad (4)$$

$$Tapped\ Bulk\ Density = mass\ of\ powder/tapped\ volume \quad (5)$$

Bulk and tapped densities

For "bulk density" estimation: 10 gram of Powder blend added in a measuring cylinder and observed the volume that taken-up by the powder.

For "tapped density": Graduated cylinder was filled by blend of powder and tapped 100 times & if any change in powder volume was observed (Qureshi *et al*., 2017).

Angle of repose (θ)

Funnel method was used to evaluate angle of repose for blends of powder. A funnel was kept on tripod stand and powder is filled in it to analyze flow pattern of powder (Qureshi *et al*., 2017).

It is calculated as; $\theta = \tan^{-1} h/r$ (6)

Where; θ: Angle of repose, r: Radius of heap, h: Height of the heap.

Physical and Chemical Analysis of Formulations (F2, F4, F6, F8 and F9)

Organolaptic Evaluation and Physical Tests

These tests were performed on the physical characteristics of the tablet that were assessed by the sense organs like; tablet size, odour, shape and colour (Hafeez *et al*., 2019). Uniformity of weight, thickness, hardness, diameter of dosage units were tested using a sample of 20 tablets. Friability was carried out using Roche friabilator. 20 tablets were taken and tested at the rate of 25 rpm up to 4 minutes and subsequently all tablets were taken out to be assessed again for weight variation with acceptable values ≤ 1% (USP, 2012).

Disintegration test

One tablet from each batch put into 6 tubes of basket rack assembly and whole assembly was placed in a 1L beaker having medium at temperature of 37±2°C. Tablets' floating was avoided by placing plastic discs on each

tube. Disintegration time for conventional directly compressed tablet is <15 minutes (BP, 2013).

Dissolution test

Apparatus-2 (Paddle Type) was used at 37±0.5°C. method specification includes 0.1 N HCl solution, Apparatus II: 100 rpm, Time: 45 min, Wave length: 263 nm. For dissolution studies 0.1N HCl solution was used to carry out percent drug release studies of all tested preparations (F2, F4, F6, F8 & F9) at 37°C ± 0.5°C at the pH of 1.2. UV-Spectrophotometer was used to measure the sample absorbance to the max of 263 nm wavelength.

Assay and content uniformity test

For this test 30 tablets were selected and 10 were assayed individually. By means of content uniformity test % recovery of formulations was calculated using in vitro analytical technique. That indicated the strength and potency of the formulation. The acceptance limit of Mebeverine HCl tablets in B.P are 95.0%-105.0% (BP, 2013).

Assay preparation

The 20 tablets Weighed and powdered. The powdered tablets were heated for 10 minutes with 0.5g of Mebeverine Hydrochloride and 0.1M *hydrochloric acid* (*HCl*) measuring 100mL on a water bath, with occasional agitation. Cooled and added adequate quantity of 0.1M (*HCl*) to make 250mL and then filter. To the filtrate of 10 mL further added 0.1M (*HCl*) adequately to make 100mL and dilute 15mL of the resultant solution upto 100mL by the same solvent. Absorbance of the solution was measured at the max of λ 263 nm, Appendix II B. The content of C25H35NO5HCl calculated and took 263 as the value of A (1%, 1 cm) up to the maximum of λ 263 nm (BP, 2013).

STATISTICAL ANALYSIS

Analysis of variance (One -Way ANOVA) SPSS 17.0 software (SPSS Inc.) with Tukey's post hoc results to observe any change in pattern of release of all test formulations in the simulated media at α = 0.05 level of significance. (RSM) 3-dimesional plots, contour plots and standard error graphs of tablet hardness were also plotted by Design Expert® Software.

Multiple point dissolution comparison

The tests were performed in 0.1N HCl (pH 1.2) in the paddle dissolution apparatus II at the 100 rpm (rounds per minute), at temperature of 37±0.5ºC, sample was collected at different time intervals of 5, 10, 15, 20, 30, 45, 60, 90 and 120 minutes. Content of (MebHCl) was observed at λ=263 nm

In-vitro release kinetics of dissolution profile

Model Independent Methods

The reference formulation was set to be used for assessing the test preparations to analyze the in-vitro data by using model independent methods *"f_1"* (Eq. 7) and *"f_2"* (Eq. 8). The *"f_2"* (Similarity factor) is used to evaluate in-vitro data for comparing the test preparations with reference one.

$$f_1 = \left[\frac{\sum_{t=1}^{n}(R_t - T_t)}{\sum_{t=1}^{n} R_t}\right] \times 100 \quad (7)$$

$$f_2 = 50 \times log\left\{\left[1 + \left(\frac{1}{N}\right)\Sigma(Rt - Tt)^2\right]^{-0.5}\right\} \times 100 \quad (8)$$

Model dependent methods

In the current study four models were chosen to estimate the release kinetics pattern of F2, F4, F6, F8 and F9 preparations in 0.1N HCl solution (pH 1.2) which are First-order Kinetics (Eq. 9), Hixon-Crowell's cube root law (Eq. 10), Higuchi's (Eq. 11) and Weibull's model (Eq.12).

$$\text{LogQ} = \text{Log } Q_o - \frac{kt}{2.303} \quad (9)$$

$$Q = kt^{1/2} \quad (10)$$

$$Q_o^{1/3} - Qt^{1/3} = \text{Khc} \times t \quad (11)$$

$$m = 1 - exp^{\left[-\frac{(t-T(i))\beta}{\alpha}\right]} \quad (12)$$

Stability studies

International Committee on Harmonization (ICH) guidelines (ICH QIA (R2) were followed for this study. Formulations were placed at accelerated states 75±5% RH and 40±2°C (3 months). Samples were collected at 0, 1 & 3 months (accelerated conditions) for batches F2, F4, F6 and F8 (table 9).

RESULTS

The main cause of this study was to prepare directly compressible Mebeverine Hydrochloride tablets by applying Central Composite Rotatable Design (CCRD). Nine preparations (F1−F9) were manufactured, kept two variables with five (5) levels in which response variables were set as disintegration time (DT) and hardness (table 3-4). Compendial and non-compendial requirements for quality control (QC) data were followed in simulated media of F2, F4, F6, F8, F9, the outcomes were assessed by Model-dependent, model-independent and statistical method (ANOVA). Samples were kept in accelerated stability on 40°C±2°C (Temperature) and 75%±5% RH (Relative Humidity) for 0, 1, 3 months. Efficacy was analyzed with determination of shelf life. The blends of powder were assessed by Hausner's Ratio, Angle of Repose (θ) and Carr's Index and as a result preparations (F1, F3, F5 and F7) could not pass the all three mentioned tests. The Mean Value in the range of lowest and highest were obtained as for Angle of Repose (θ) 27.58º±1.23º-52.38º±0.85º, Hausner's Ratio 1.08±0.021 -1.41±0.02 and Carr's Index 9.71%±0.59% -28.19% ±1.58% (table 2).

The test formulations (F2, F4, F6, F8 and F9) were evaluated for both Pharmacopeial and non-pharmacopeial

Table 1: Experimental considerations of compressibility (USP, 2012)

Flow Properties	Angle of Repose (θ)	Hausner's Ratio	Carr's Index (%)
Excellent	25-30	1.00-1.11	≤10
Good	31-35	1.12-1.18	11-15
Fair	36-40	1.19-1.25	16-20
Passable	41-45	1.26-1.34	21-25
Poor	46-55	1.35-1.45	26-31
Very Poor	56-65	1.46-1.59	32-37
Extremely Poor	>65	>1.60	>38

Table 2: Powder blend evaluation of test and reference preparation

Batch Code	Angle of Repose (θ)	Hausner's ratio	Carr's Index (%)
F1	49.07º ± 2.52º	1.38 ± 0.02	28.19 ± 1.58
F2	27.58º ± 1.23º	1.08 ± 0.021	9.71 ± 0.59
F3	52.38º ± 0.85º	1.41 ± 0.02	27.67 ± 1.24
F4	33.74º ± 0.57º	1.18 ± 0.70	13.25 ± 1.22
F5	31.83º ± 0.73º	1.14 ± 0.02	13.68 ± 1.24
F6	37.27º ± 1.68º	1.22 ± 0.05	19.53 ± 0.84
F7	38.65º ± 0.98º	1.22±0.03	19.16 ± 0.96
F8	39.48º ± 1.07º	1.21 ± 0.02	19.72 ± 0.96
F9	32.99º ± 1.32º	1.14 ± 0.01	12.66 ± 1.25

Table 3: Composition of mebeverine HCL directly compressible tablets using CCRD

Code	Type	B: Crospovidone (%)	B: Avicel (%)	(Avicel 102) (mg)	Cros-Povidone (mg)	Mg. Stearate (mg)	Drug (mg)	Tablet (mg)
F1	Fact	3	30	227.14	22.71	15.14	135	400.00
F2	Fact	9	30	193.90	58.17	12.93		
F3	Fact	3	55	242.92	13.25	8.83		
F4	Fact	9	55	220.83	36.14	8.03		
F5	Axial	1.757359	42.5	243.47	10.07	11.46		
F6	Axial	10.24264	42.5	205.74	49.58	9.68		
F7	Axial	6	24.82233	200.41	48.44	16.15		
F8	Axial	6	60.17767	233.90	23.32	7.77		
F9	Center	6	42.5	223.02	31.49	10.50		

Table 4: Levels of variables for optimization in tablet manufacturing

Code	Variables	Level of Variables					
		-1 (%)	+1 (%)	-α (%)	+α (%)	0 (%) (Mean)	Standard Deviation
X_1	Crospovidone	2	6	1.17	6.83	4	1.88
X_2	Avicel	35	60	29.82	65.18	47.5	11.78

tests. The mean values from lowest to highest were found as for weight of tablets 402.75±7.08mg - 405.8±7.44mg, thickness range 3.40mm±0.04mm -3.30mm±0.09mm, & diameter 8.47mm±0.15mm -8.67±0.18mm and mean hardness range was 8.60kg±0.16kg -9.18kg±0.45kg (table 5) and Disintegration Time (DT) was found as 6 minutes to 11 minutes. The % friability of the tested preparations was calculated in the range of 0.63% -0.85%. Random sampling of tablet for test of fineness for dispersion was also performed. The Assay was obtained in the range of 100.66%±0.41% -103.506%±0.45% (table 5). Various response diagrams were plotted and evaluated (table 6; fig. 1-2). Dissolution Profile Comparison (DPC) was also compared for the assessment of release behavior of the drug by using 0.1N HCl solution. Moreover a comparison of dissolution was established with reference formulation and statistically analyzed by ANOVA. The drug release was observed by Difference Factor (*f*) and Similarity Factor (f_2). All outcomes were within acceptable limits. Findings revealed that the profiles of dissolution of test

Table 5: Physico-chemical tests of various mebeverine HCl tablets batches

Batch	Weight (mg) ±SD	Thickness (mm)±SD	Diameter (mm)±SD	Hardness (kg) ±SD	Friability (%) n=10	Disintegration (min)	Assay Test Mean ±SD	Content Uniformity Mean ±SD
F2	403.4±7.21	3.30±0.09	8.47±0.15	8.91±0.36	0.79%	6	103.33±1.10	101.71±1.73
F4	405.25±7.62	3.40±0.04	8.67±0.18	9.04±0.42	0.85%	9	100.96±0.92	100.59±0.20
F6	405.8±7.44	3.36±0.04	8.54±0.18	9.13±0.48	0.75%	7	100.66±0.41	99.323±1.31
F8	402.75±7.08	3.38±0.03	8.60±0.18	9.18±0.45	0.63%	11	101.97±1.91	100.41±0.08
F9	405.1±6.78	3.34±0.08	8.60±0.17	8.60±0.16	0.77%	7	103.506±0.45	102.84±0.15

Table 6: Analysis of variance (ANOVA) for mebeverine HCl tablets

Factors	Sum of squares	df	Mean square	F-Value	P-Value
Hardness					
Model	4.539	2	2.269	13.059	0.006
A-A(X1)-Crospovidone	0.037	1	0.037	0.216	0.658
B-B (X2)Avicel	4.501	1	4.501	25.902	0.002
AB	-	-	-	-	-
A^2	-	-	-	-	-
B^2	-	-	-	-	-
Residual	1.042	6	0.173	-	-
Cor Total	5.582	8	-	-	-
Disintegration Time					
Model	52.516	5	10.503	7.206	0.067
A-X1-Crospovidone	45.463	1	45.463	31.192	0.011
B-B Avicel	3.664	1	3.664	2.513	0.211
AB	1	1	1	0.686	0.468
A^2	0.409	1	0.409	0.280	0.633
B^2	2.227	1	2.227	1.528	0.304
Residual	4.372	3	1.457	-	-
Cor Total	56.888	8	-	-	-

Table 7: Difference Factor (f_1) & Similarity Factor (*f*2) of All Preparations

Formulations	Difference Factor (f_1)	Similarity Factor (*f*2)
F2	1.91	91.91
F4	5.90	59.37
F6	3.10	73.25
F8	3.61	67.76

Table 8: Release kinetics of mebeverine HCl formulations

Formulations	First Order		Higuchi		Hixon-Crowell		Weibull Model		
	r^2	K_1 (h_{-1})	r^2	Kh (h ½)	r^2	KHc ($h^{-1/3}$)	r^2	β	α
F2	0.939	0.102	0.602	8.679	0.989	0.016	0.966	0.772	5.551
F4	0.933	0.077	0.717	9.230	0.995	0.012	0.970	0.747	6.541
F6	0.925	0.090	0.659	8.756	0.993	0.013	0.974	0.720	5.383
F8	0.981	0.087	0.602	9.195	0.992	0.017	0.985	0.886	8.591
F9 (Reference)	0.945	0.104	0.593	8.512	0.993	0.016	0.977	0.760	5.326

preparations were shown as alike with the reference formulation (table 7). The r^2 value for First-order kinetics was (0.981), for Higuchi's model (0.717), for Hixon-crowell's model (0.995) and for Weibull's model (0.985) (table 8). All formulations followed Weibull's model. The Trial formulations F2, F4, F6 and F8 were also studied on accelerated conditions (40±5ºC / 75±5% RH) for stability test and validity of the formulations in months were also determined as for F2 = 39.29, F4 = 39.56, F6 = 39.49 and F8 = 35.53 (table 9). The F2 batch was found the best optimized formulation. The best Pharmaceutical features were observed in F2 preparation with optimal micromeritic and physico-chemical features and rapid disintegrating time of 6 minutes.

Table 9: Accelerated stability profile of all test formulations

Parameters	Periods (Months)	Formulations			
		F2	F4	F6	F8
Assay (%) (n=3)	0	103.33±1.106	100.96±0.92	100.66±0.41	101.97±1.901
Hardness (n=10) (kg)		8.91 ± 0.36	9.04 ± 0.42	9.13 ± 0.48	9.18 ± 0.45
Dissolution Test (%) (n=3)		102.32±0.07	100.66±0.12	99.57±0.21	100.18±0.26
Disintegration Test (Mins.)(n=6)		6	9	7	11
Assay(%)(n=3)	1	102.89±1.74	100.08±2.16	100.17±1.37	101.43±1.25
Hardness (n=10) (kg)		8.79±0.87	9.20±0.69	9.21±0.98	9.98 ±0.74
Dissolution Test (%) (n=3)		101.67±1.45	100.17±1.07	100.43±1.32	100.58±1.59
Disintegration Test (Mins.) (n=6)		7	9	8	12
Assay (%) (n=3)	3	102.01±2.24	99.78±2.61	100.01±1.05	100.98±1.34
Hardness (n=10) (kg)		8.81±0.37	9.21±0.58	9.17±0.78	9.91±0.87
Dissolution Test (%) (n=3)		100.13±1.81	99.98±1.39	100.05±1.37	100.29±1.13
Disintegration Test (Min) (n=6)		8	10	9	12

Table 10: Comparison of study parameters with reported literature

Parameters	Previous literature (Palkhede et al., 2012)	Current study	Parameters	Previous literature (Palkhede et al., 2012)	Current study
Crospovidone (%)	2-4	1.7-10	Friability (%)	0.72-1.5	0.63-0.85
Avicel (%)	21-23	24-60	Disintegration (sec)	36-44	6-11
Hauser ratio	1.08-1.51	1.08-1.41	Assay (%)	97-98	100.66-103.5
Carrs index (%)	7.66-33.8	9.71-28.19	Drug release (%)	96-98	99.57-102.32
Angle of Repose (^{0})	24.03-37.08	27.58-52.38	Hardness (Kg/cm^2)	2.85-3.27	8.60-9.18

DISCUSSION

Many statisticians/researchers in pharmaceutical development have used variety of statistical designs to manufacture a tablet such as, full factorial design & CCRD (Central Composite Rotatable Design) (Bhargav e al., 2017). In this research CCRD with Software Design Expert® (Version 7.0, Stat-Ease Incorporation) was applied. Amount of active agent (Mebeverine HCl) was taken constant as 135mg (table 3). For making uniform preparation, always consider the micromeritic attributes of blends of powder. To improve quality of tablet the flow property can be modified by size of particle, electrostatic charges, shape, moisture content and exterior structural features of particle (Qureshi *et al*., 2017).

Experimental analysis and standard values of Angle of repose (θ), Hausner's Ratio and Compressibility Index are depicted in table 1. Flow characters of powder showed diversity that revealed in the results obtained. Optimized product mean values of Angle of Repose F2 (27.58º±1.23º), Hausner's Ratio, F2 (1.08±0.02), Carr's Index F2 (9.71%±0.59%) were shown satisfactory and in good agreement with related studies (table 2). Shah *et al*., in 2014 and Ali *et al* in 2019 also studied and reviewed mafenamic acid and Meloxicam mixtures in variable proportions of excipients using powder flow characterization techniques (Shah *et al*., 2014; Ali *et al*., 2019; Amin *et al*., 2012). In current investigation among all observed values of test preparations, formulation F2 with 193.90mg of Avicel have shown hardness (8.91±0.36kg), while as F8 contains Avicel 233.90mg was observed with maximum hardness as 9.84±0.34kg (table 3). The study revealed that if concentration of Avicel (microcrystalline cellulose) increases as filler/binder the hardness of tablet *al*so increases. To increase the mechanical strength of tablets with direct compression numerous excipients are presented locally. These materials give adequate compactability and flowability and reveals excellent rate of dissolution that is required for formulation of tablets with instant release profile (Maja *et al*., 2012). Erga *et al* in 2018 used the disintegration time and hardness as response variable and found significant relation in formulation of paracetamol fast dispersible tablets (Eraga *et al*., 2018). (RSM) 3-dimesional plots, contour plots and standard error graphs of tablet hardness were also plotted by Design Expert® Software. (fig. 1A: 2D). In this study the normal probability plot (fig. 1A & 2A) is used as a graphical means to compare a data set through the regular distribution. We can utilize it with the standardized residual of the linear regression model and observe if the error term ϵ is distributed normally. Data points must be almost linear. A non-linear pattern (such as an S-shaped curve) shows non-normality in the error term, it might be fixed by a transformation. However in current investigation no transformation of data was carried out. Model F-value of 13.06 shows the model is significant.

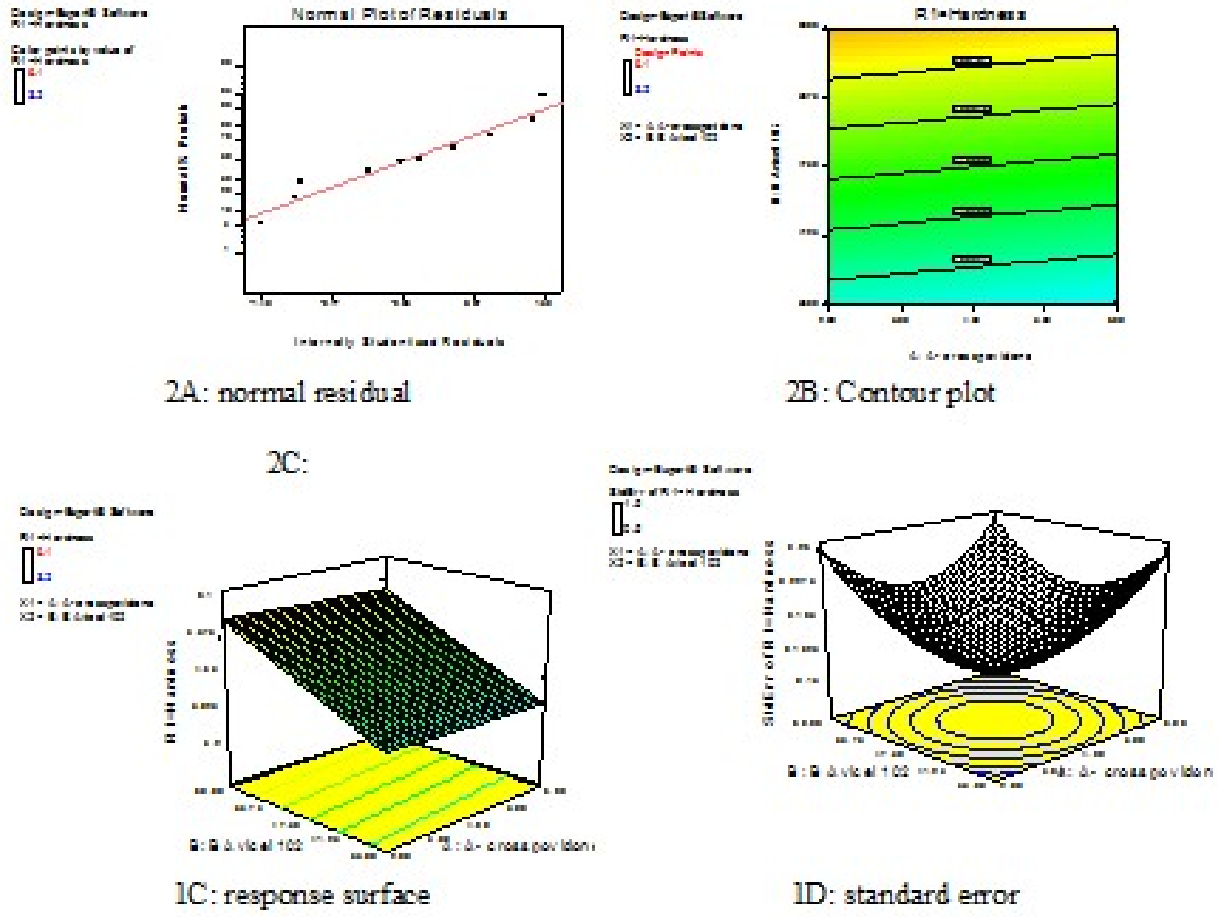

Fig. 1(A-D): Graphical Response Surface Methodology (RSM) Effects of Excipients on Hardness of Mebeverine HCl Tablets

There is just a 0.65% probability that a "Model F-Value" this large might happen because of noise. Values of "Prob > F" less than 0.0500 show that model terms are significant. For hardness case A are significant model terms (table 6). While for Disintegration case B are significant model terms (table 6). The contour plot (fig. 1B & 2B) was used as a two-dimensional (2D) illustration of the response plotted against combinations of numeric factors and/or mixture components. It illustrates the correlation between the mixture components, responses, and/or numeric factors. Design-Expert shows any actual point in the design space revealed. Through replicating center points, one can acquire an excellent prediction power at the middle of experimental area. Design-Expert contour plots are highly interactive. A three-d view of the response surface was used to evaluate weather response changes as a function of the two factors selected (fig. 1C &2C). If the coordinates comprise actual design points, these will be displayed. Moreover standard error plot reveals how variance linked with prediction modification over design space (fig. 1D & 2D). So here the central composite design (CCD) gives fairly specific predictions over a broad area around the 6 center points. Moreover, observe the circular contours (fig. 1B & 2B), this shows the required quality of rotatability evenly defined predictive power at equivalent distance from the center point of this RSM design. In current invest.igation, the outcomes showed as amount of crospovidone increased the time to disintegrate a tablet decreased in all studied formulations. Previously, non-modified disintegrants were in use to speed up disintegration, however nowadays a fast working superdisintegrant is chemically modified, characteristically by cross linking the organic chains of polymeric molecules. (Gandhi and Semimul 2019). One of study proved that determined amount of disintegrants in preparation will result in improved deaggregation of a tablet (Ali *et al*., 2019). Different physical parameters are responsible for a tablet to come into small fragments such as; friability, hardness, porosity of tablet and disintegration (Martinez *et al*., 2019; Pabari *et al*., 2012). All preparations passed test for disintegration, and analyzed within limit as 6 to 11 minutes for F2 (6 min) (table 5). Assay test observations found within range. While mean values of assay for F2 was calculated to be 103.33%±1.106% (table 4). One study using floating matrix technique to formulate matrix and floating raft

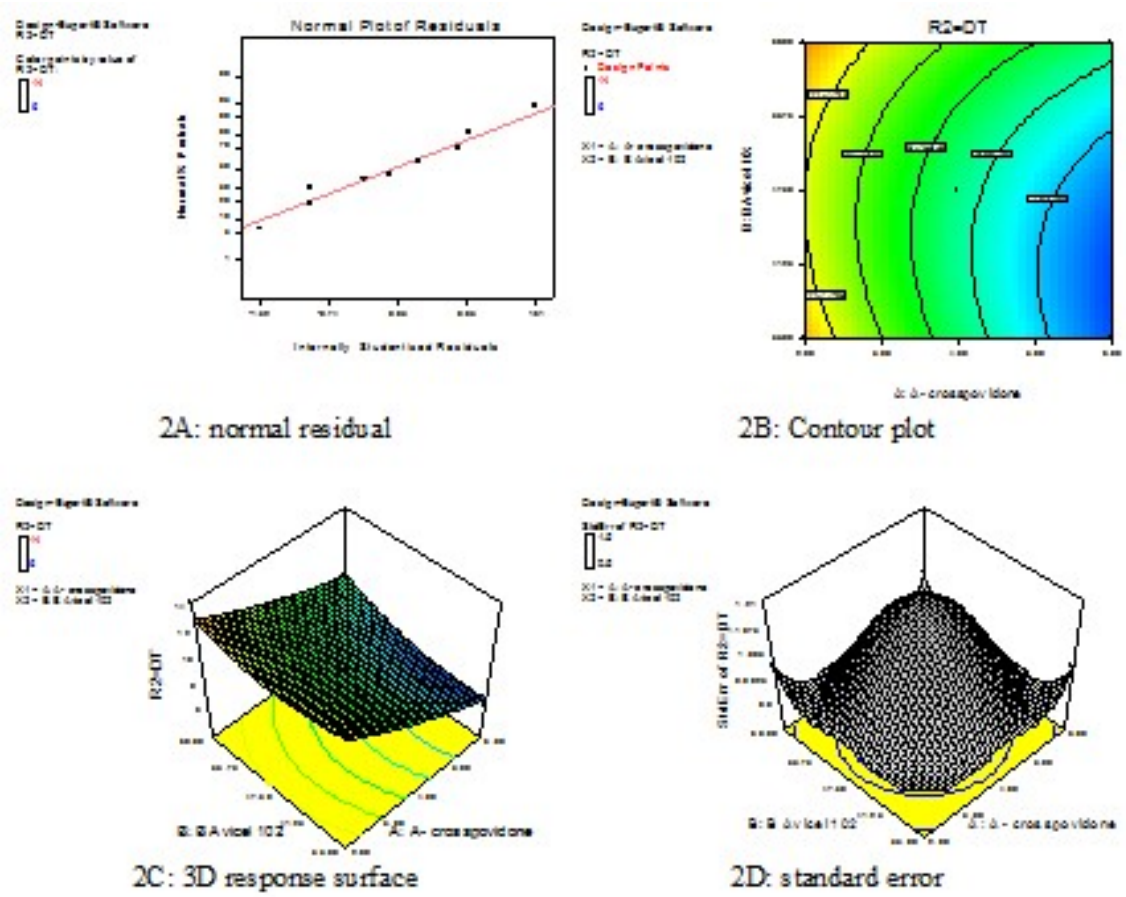

Fig. 2(A-D): Graphical Response Surface Methodology (RSM) Effects of Excipients on Disintegration of Mebeverine HCl Tablets

(FR) system of Mebeverine HCl (MbH) and evaluated diverse characterstics of excipients to produce floating behavior and control release profiles. The optimized FT-10 and FRS-11 floaing time was in order of 34±5 sec and 15±7 sec and bouncy period maximum of 12hours. Similar Cmax were calculated for marketed and FT-10 and an inclined trend was measured in FRS-11 maximum concentration. Values of Tmax were in sequence of 2.167-3.33hrs (Mohamed *et al*., 2017). *In-vitro* dissolution profile is very important to formulate and optimize a preparation for assessing the release behavior of tablets. Multiple point's assessments are more accurate than single point dissolution data (Ali H *et al*., 2013). The reference formulation was set to be used for assessing the test preparations to analyze the in-vitro data by using model independent methods *"f_1"* (Eq. 7) and *"f_2"* (Eq. 8). The *"f_2"* (Similarity factor) is used to evaluate in-vitro data for comparing the test preparations with reference. In previous studies Amlodipine Besylate tablets were studied for Model Independent method (Ahsan SF *et al*., 2019). Values of *"f_1 and f_2"* for batch F2 was found in order of 1.91 & 91.91 (table 7). It was also assessed that all test formulations having similarity with reference product and found that testing values of *"f_1"* (0-15) & *"f_2"* (50-100) lies in range (table 7). In this study the "r²-values" (Co-efficient of regression) were calculated and for First-order kinetics it was found in range of 0.925-0.981" $k_1(h^{-1})$ Values" for F2 were (0.102), F4 (0.077), F6 (0.090), F8 (0.087) and reference F9 (0.104) (table 8). Higuchi's and Hixon-Crowell models are very effective for dissolution analysis as kinetics model (Shah *et al*., 2017). By adopting Higuchi's model r²-values" were comparatively low, but r²-values" obtained by applying Hixon-Crowell model are fitted suitability in order of 0.992-0.989. In a research Higuchi's model for release profile was found fit for the product of diclofenac sodium (A. Hafeez *et al*., 2019). However Weibull's model of kinetics have shown model fit values of r²-values" 0.966-0.985, and β values in between 0.720-0.886 which has shown shape parameter curves as parabolic (b<1) = (table 8). Some Scientists worked on flurbiprofen in-vitro release kinetics and stability profile and found that all tested formulations adopt the weibull's model (Shah *et al*., 2017). The F2 formulation was chosen as the excellent ideal preparation on the basis rapid disintegration (6 minutes), excellent % dissolution (102.32±0.07%) with the content of drug as (101.71±1.73%). International Committee on Harmonization (ICH) guidelines (ICH QIA (R2) were

followed for stability study. Trial preparations of F2, F4, F6 and F8 have been found within acceptable values (table 9). No observable change was noted in tablets physical appearance. Shelf life was determined by using R.Gui version 2.12 (Shah *et al*., 2017). All software generated data is also obtained. The values for Shelf Life in months are F2 (39.29545), F4 (39.56644), F6 (39.49108) and F8 (35.53832) (table 9). In another study Mebeverine Hydrochloride fast disintegrating formulations were prepared using different super disintegrates by Palkhede *et al*., 2012 and their physicochemical and micromeritic parameters were compared with presented study (table 10). In this study CCRD was used to design the formulations. Earlier previous literature reported formulation hardness in the range of 2.85 to 3.27kg/cm^2 (Palkhede *et al*., 2012). While presented study has comparatively high values of hardness that may be due to high concentration of filler and binder. Assay and drug release values are in good agreement for both trials. Friability values are comparatively better in our investigation up to maximum 0.85%, while micromeritic results are also comparable to each other.

CONCLUSION

There is a huge requirement for improved pharmaceutical structure as precisely accurate formulation, permitting simplicity in manufacturing process and reduced costs like that of ordinary tablets. To satisfy clinical requirements, formulators have to give impressive exertion to building up a novel tablet designs for per oral route, with rapid breaks down and disintegration properties and required quality features. Exclusive market needs can be addressed by an immediate release formulation with better revenue generation, likewise focusing on underserved and under-treated patient populaces. The present research study can conclude that by adopting direct compression method for tablet manufacturing, the process to become faster and made the product more economical. Optimized preparations were assessed as valid and also indicated that response surface methodology (RSM) provides the prudential optimized preparations with judicious concentration of superdisintegrants and filler binders to effect disintegration, release and compressibility in satisfactory and stable manner.

Study limitations and future research directions

This study was mainly focused on *in vitro* assessment and stability concerns of directly compressible formulations. In-vivo study may be conducted in future and considered as limitation of presented data. Quality by design approaches may further strengthen this approach.

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