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Original Research Article

STUDY OF POWDER AND TABLETING FUNCTIONALITY TOWARDS EVALUATION AND CHARACTERISATION OF BARETab® PH (ALL IN ONE EXCIPIENT) AS A SUBSTITUTE OF CONVENTIONAL PHYSICALLY MIXED MICROCRYSTALLINE CELLULOSE, CROSCARMELLOSE SODIUM, SILICON DIOXIDE AND PURIFIED TALC IN A PCM FORMULATION

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Abstract: BARETab® PH is a multi-functional ready to use premixed, co-processed ingredient for direct compression (DC) formulations. It is a combination of selective, largely used excipients for DC. Direct compression is the most widely used tableting method because of the simple manufacturing process with higher output in a shorter time. In DC formulations, the major disadvantage is due to heterogeneous mixture of excipients and API. Mostly APIs have poor flowability and compressibility, which cause weight, hardness variation, high friability and unequal API distribution in the tablets. In general, excipients and APIs have different particle size which makes heterogeneous mixture challenging. Fine particles of API and excipient cause physical defects like sticking, capping and lamination in formulations. BARETab® PH can solve all these problems primarily due to its homogeneous mixing, larger surface area and superior flowability which carries the API and allows equal distribution in the tablets. BARETab® PH facilitates better uniformity, higher tablet hardness, shorter disintegration time and eliminates physical tableting defects. In this study, we have produced Paracetamol (PCM) tablet by direct compression with improved tablet properties and shortened manufacturing time when compared to the wet granulation method

Keywords: Co-Processed Excipient BARETab® PH, True density, Compressibility, SEM, Surface area, Paracetamol DC tablet.

Introduction: Direct compression is most widely used method in formulation industries because it's simple and cost effective [1]. To make tablets by direct compression, excipient performance should be excellent in terms of flowability, compressibility, improved mixing properties and equal quantity of API being carried in the die cavity during tabletting [2]. Co-processed excipients like HiCel™ SMCC, HiCel™ CE 15, Avicel DG, Avicel HFE are known as ideal choice for direct compressible tablets [3]. Co-processed excipients improved

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API blend properties and enhanced final product quality included productivity and yield performance [4].

Lately, few excipient manufacturers have introduced excipient premix in the formulation market. Excipient premix is a combination of different excipients which is require to make direct compressible tablet formulations [5]. Sigachi, a significant excipient player in India has launched an excipient multi-functional premix for DC tablet formulation in the market under brand name BARETab®. BARETab PH is a very homogeneous co-processed ingredient with a larger surface area. It results in a very good performance even when combined with poor flowable APIs. BARETab® PH carries API in high and even low dosage formulations, making it the most versatile multi-functional, ready-to-use premix for direct compression of tablets [6]. BARETab® PH is an innovated combination of excipients that contains an effective binder/filler, glidant, disintegrant and lubricant in appropriate quantity and manufactured through a proprietary co-processing technology [7]. BARETab® PH is an ingredient that allows the reduction of the manufacturing time and costs and increases productivity [6].

BARETab® PH expedites the development of solid dosage forms. It minimizes the challenges faced by formulators during the manufacturing of tablets by direct compression. BARETab® PH is a single ingredient with multiple functions, thus reducing the inventory burden of various excipients [8]. BARETab® PH has advantages when used in the continuous production of tablets, and improves the production yield[6].

In this study, we have compared how excipient premix is better than physical mixing by characterization, SEM and Surface area. and we have made direct compressible tablet formulation with most challenging pharmaceutical active ingredient Paracetamol and evaluated its in-vitro properties like weight uniformity, tablet hardness, friability, in-vitro disintegration and dissolution profile.

Material and method

Material: BARETab® PH, HiCel^{TM} filler, binder and HiLose^{TM} disintegrant manufactured at Sigachi Industries Ltd. in Dahej, Gujarat. Glidant purchased form Nikon Corporation, Wacker Germany, lubricant purchased from Gangotri Inorganics (P) Ltd and Paracetamol purchased form Farmson pharmaceuticals, Gujarat.

Method:

BARETab® PH and Physical Mixing Sample Preparation: BARETab® PH is manufactured by co-processing method. It contains binder, filler, glidant, disintegrant and lubricant. Physical mixing sample prepared with the same ingredients and with the same quantity. Weigh accurate quantity of binder, filler, glidant and disintegrant, blend the material using Reva blender (Model TRMIX-20) for 10 minutes after that add accurate quantity of lubricant and blend in the mixer again for 5 minutes [8].

Scanning electron microscope Analysis: Take approximate 1 to 2 milligram from each sample. Both samples were mounted on double sided taped on aluminum stabs and sputter coated with platinum with the help of auto fine coater JEOL (JFC.1600). Micrographs were taken at appropriate magnification and particles surface visualization detailed analyzed by scanning electron microscope JEOL (JSM.76000 F) [9].

BET Surface Area Analysis: Take 0.1380 g each sample in sample cell and charge nitrogen gas at low pressure dose 10.00 cm^3/g STP and -195 .73 0C temperature [10]. Surface area of both samples were analysed by using Micromeritics surface analyser at Shah-Schulman Centre for Surface Science & Nanotechnology Dharmsinh Desai University, Nadiad, Gujarat.

Ture density: Take 3.4480 g each sample in small size cell, charge helium gas at 19 psi pressure and 23 ^{0}C temperature [11]. True density of both samples was analysed by using Pycometer, Quantachrome instruments (upyc

1200e v5.06), at Anton Paar application lab, Gurugram, Haryana.

Untapped density: Untapped bulk density analysed by Scott volumeter. Weight empty cup, place it under the chute and 10g of each sample is poured into funnel through volumeter, at a rate suitable to prevent clogging, until the cup overflows. Level the excess powder and weight the filled cup[12].

Tapped density: Tapped density is determined by placing a graduated cylinder containing a known mass of final blend powder on a mechanical tapper apparatus (Model No. ETD 1020) which is operated at fixed number of tapped (500) until powder bed reached a minimum volume [13].

Hausner's ratio: It is indirect index for ease of measuring powder flow. Lower Hausner's ratio (<1.25) indicates good flow property [13].

Hausner's Ratio = Tapped density/ Bulk density

Compressibility: Compressibility known as carr's index. Based on the apparent bulk density and the tapped density. Percentage compressibility is calculated by below formula [13]

Compressibility = Tapped density - bulk density ×100/ Tapped density

Angle of repose: Angle of repose obtained between freestanding surface of powder heap and the horizontal plane. It was determined by using the fixed funnel method. 20 gm of final blend powder was poured into funnel keeping the orifice of the funnel blocked by thumb. When powder was cleared from funnel then the peak height was measured [13].

Table 1: Powder characteristics indicative of the powder quality [14]

Types of flow	Angle of repose (°)	Compressibility index (%)	Hausner's ratio
Excellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-56	32-37	1.46-1.59
Very-very poor	>66	>38	>1.60

Particle size distribution analysis: Particle size of both samples were analysed at Cubic Analytical Solution, Ankleshwar, Gujarat using lesser diffraction (Malvern instrument, Mastersizer v3.63) [15].

Paracetamol blend preparation

Paracetamol blend with BARETab® PH: Weigh accurately BARETab® PH and Paracetamol using digital weighing balance (Mettler Toledo, ME303/A04), transfer both material into powder blender (Reva Pharma machinery, TRMIX-20) and blend the both material for 8 to 10 minutes, material is ready for tabletting.

Paracetamol blend with physical mixing: Weigh accurately binder, filer, glidant and disintegrant quantity using weighing balance (Mettler Toledo, ME303/A04) and transfer in to powder blender (Reva Pharma machinery, TRMIX-20), blend the all ingredient for 5 minutes after that add paracetamol into mixer and blend again for 8 to 10 minutes. At last add lubricant into the mixer and blend the material again for 3 minutes, material is ready for tabletting [16].

Table: 2 Paracetamol 500 mg Tablet manufacturing details

Ingredient Name	Quantity (W/W %)	
	BARETab® PH	Physical mixing
Paracetamol	55.56	55.56
BARETab® PH	44.44	--
Physical mixing	--	44.44

Paracetamol Tablet compression: 900 mg tablets were manufactured by using 10 station Proton Mini Press (MINI PRESS 10 "D") using

D tooling dies and punches with 15 mm diameter. Both samples Paracetamol tablet manufactured at the same compression force [17].

Physical appearance: The general appearance of both samples' paracetamol tablet was studied visually in shape, colour, texture.

Weight variation: Weight variation test was performed by weighing 10 tablets individually using four-digit digital weighing balance (Mettler Toledo, MS304S/A01), calculating the average weight and comparing the individual tablet weight to the average. The weight variation test would be a satisfactory method of determining the drug content uniformity of the tablets [18].

Thickness: The tablet thickness was calculated by Vernier callipers using sample size of 10 tablets. Tablets were put in between two jaws vertically and the thickness measured [18].

Hardness: Randomly 10 tablets were taken from each sample. Electronic digital hardness test machine (TH1050 M) was used to analyse tensile strength of tablets. Single tablet was placed between two anvils, force was applied to the anvils, and the tensile strength that was just required to break the tablet was recorded. Finally, the reading was noted in Newton [19].

Friability: 10 tablets were taken and weighed by using electronic digital balance which was considered as the initial weight. All the tablets were placed in the drum of friability tester (FT1020) and allowed rotate 100 times at 25 rpm. After 100 revolutions, 10 tablets were removed and re-weighed which was considered as the final weight. The percentage friability was calculated by below mention formula. As per USP, the tablets should not lose more than 1% of their total weight [20].

$$\text{Friability (\%)} = \frac{\text{Initial weight(mg)} - \text{Final weight(mg)}}{\text{Inital weight (mg)}} \times 100$$

***In vitro* disintegration time:** Disintegration time of paracetamol tablets were analysed by using tablet disintegration tester (Labindia, DT 1000) at 37±2°C in 800 ml Demineralized water. Six tablets were taken and one tablet was introduced in each tube, disk was placed and basket was positioned in one litre beaker containing 37±2°C temperature of water. Note down tablet breaking time. Noted the time when the tablet broke down into smaller particles [21].

***In vitro* dissolution profile:** Paracetamol released profile was analysed by using dissolution test apparatus (Labindia, DS 8000) and followed by USP method, apparatus type 2 (paddle), speed 50 rpm in 900 ml of pH 5.8 phosphate buffer (Potassium di-hydrogen ortho phosphate) solution at 37±2 °C medium temperature. Randomly select 6 tablet and one tablet introduced in each beaker of dissolution. 5 ml Sample were withdrawal from each beaker at different time intervals 5, 10,15, 20, 25, 30, 35, 40 minutes. Samples filter with Whatman filter paper (42). Take 1 ml sample from the beaker and transfer into 10 ml of volumetric flask and makeup the volume up to the mark. Repeat the same procedure for all remaining 5 tablets containing samples. Take sample and standard absorbance using UV Spectrophotometer (Shimadzu model no-1900) at λ=257nm wavelength. Calculate paracetamol released profile with the help of below mention formula and calculate average paracetamol release profile [22].

$$\text{Amount of API released (mg)} = \frac{\text{Conc.of released drug} \times \text{dilution factor} \times \text{Volume of dissolution medium}}{1000}$$

$$\text{Drug released (\%)} = \frac{\text{Amount of drug released}}{\text{Dose of drug}} \times 100$$

Result and discussion

Scanning electron microscope Images: BARETab® PH single particle contains binder, filler, glidant, disintegration and lubricant. Which gives homogenous mixing. Where as in Physical mixing SEM images show different-different particles and morphology which creates heterogenous mixing.

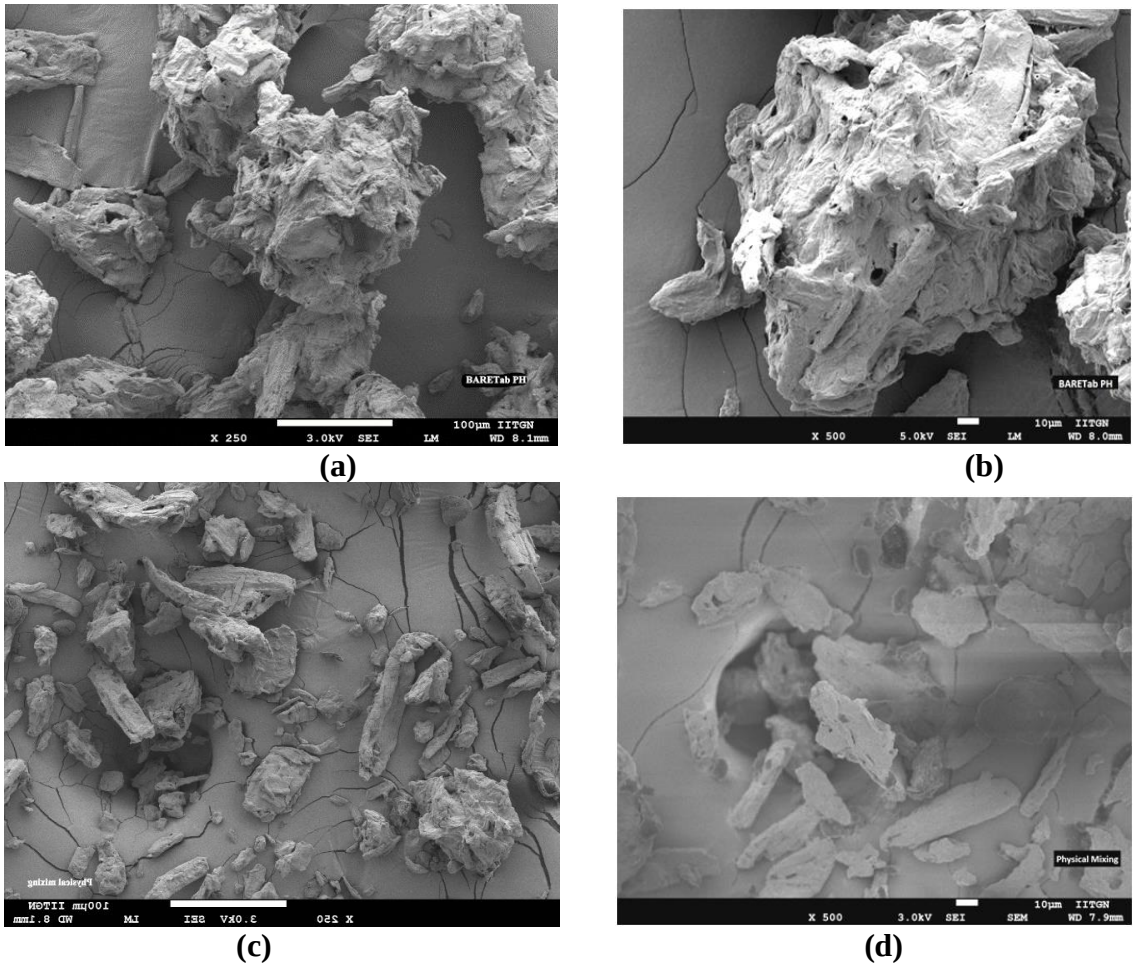


Fig :1 Scanning electron microscopic images (a)&(b) BARETab® PH and (c) &(d) Physical mixing

BET Surface area: The BET specific surface areas of BARETab® PH was 4.8 m^2/g and physical mixing 3.7 m^2/g. BARETab® PH has larger BET specific surface area as comparative to physical mixing, which is an increase of nearly 30% over the physical mix particles. These differences are not in relation with the particle size distributions. It is calculated from laser diffraction. The changes in the specific surface area are probably correlated with the roughness of the particles' surfaces. However both material particles have different surface which are shown in Fig:1 (a),(b),(c) and (d) . BARETab® PH particles have rough surface area and have larger BET specific surface area. Larger surface area results in higher interarticular bonds which impact on tablet hardness. BARETab® PH have more tablet hardness due to the presence of interparticle bonds and the force of these bonds helps to achieve higher tablet hardness.

True density: True density is the density of the solid material excluding the volume of any open and closed pores. Depending on the molecular arrangement of the material, the true density can equal the theoretical density of the material and therefore be indicative of how close the material is to a crystalline state or the proportions of a binary mixture. The true density of BARETab® PH was higher at 1.5417 g/cc than physical mixing0.9854 g/cc.

Untapped density and Tapped density: BARETab® PH has untapped density 0.36 g/cc and tapped density 0.47 g/cc, whereas physical mixing has 0.33 g/cc untapped density and 0.46 g/cc tapped density. Higher untapped density and lower tapped is require for direct

compression formulation and it helps to increase blend flowability.

Hausner ratio and Compressibility index: Hausner's index and compressibility index are considered as indirect measurements of powder flowability, The Hausner index is indicative of interparticle friction, while the Compressibility index shows the aptitude of a material to diminish in volume. As the values of these indices increase, the flow of the powder decreases. Then values obtained for both the materials shown in Table :1. Whereas high value is an indication of poor flow of the material. This can be happen due to smaller particle size. BARETab® PH has 1.30 hausner ration and 23.11 compressibility index where as physical mixing has 1.39 hausner ratio and 28.26 compressibility index. Lesser hausner ratio and compressibility index is useful for achieving good quality of tablets.

Angle of repose: The flow properties of powders are essential in determining the suitability of a material as a direct compression excipient. Increasing value is an indication of decreasing flowability. BARETab® PH has excellent flowability which is represented by angle of repose, BARETab® PH has 28° and physical mixing has 35° angle of repose. Due to small particles size physical mixing has poor flowability. Less angle of report of excipients help to improved API flowability, which impact the final tablet quality.

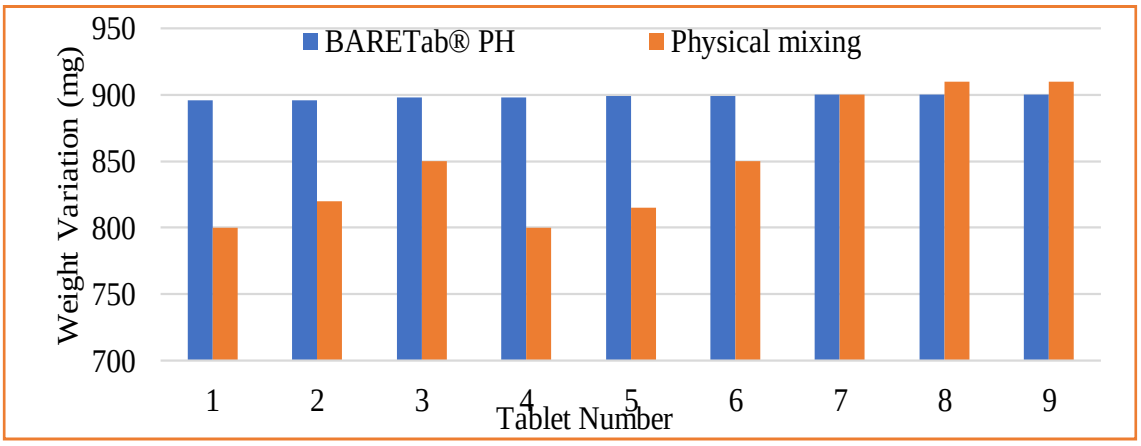
Particle size analysis: Particle size play a very important role in direct compression formulation. Bigger particles size increase powder flowability and it helps to carry equal API quantity in to the all tablets. BARETab® PH average particle size is 120 µm and physical mixing is 102 µm. For Direct compression method excipient average particles size is desirable to be more than 110 µm.

Tablet compression: BARETab® PH containing Paracetamol tablet compressed properly and tablet machine ran smoothly. However, physical mixing containing paracetamol tablet was not made properly and machine did not run smoothly due to poor flowability and heterogeneous powder blend. Maximum tablets were rejected in visual defects.

Physical appearance: All tablets are white colour with 15 mm diameter and round shaped. Paracetamol tablets containing BARETab® PH are free all tablets defects however, paracetamol tablet containing physical mixing have sticking, capping, lamination defects on tablet surface.

Weight variation: We have found weight uniformity in BARETab® PH containing paracetamol tablets as compared to physical mixing containing paracetamol tablet. Due to larger particles size, excellent flowability BARETab PH maintained equal die-cavity filling resultant found minimum tablet weight variation and paracetamol uniformity in all tablets. Average weight mentioned in table 3.

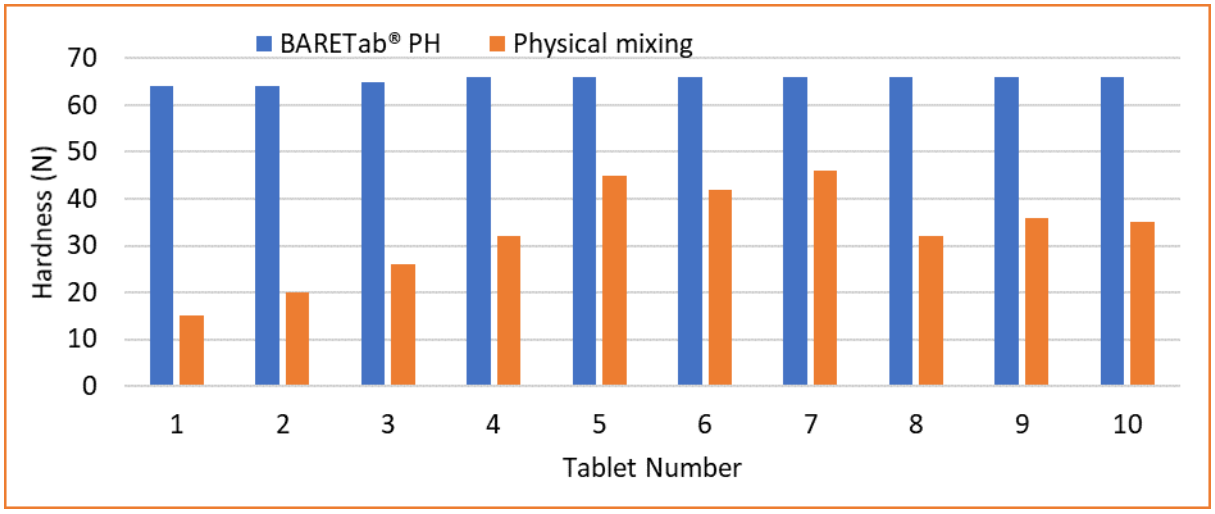
Fig: 2 weight variation comparison of paracetamol tablet made with BARETab® PH and physical mixing



Thickness: BARETab® PH and physical mixing containing paracetamol tablet have 5.5 mm thickness.

Hardnes: Paracetamol tablet made with BARETab® PH having more tablet hardness as comparative to paracetamol tablet made with physical mixing. Average hardness of both samples mentioned in Tablet:3.

Fig:3 Hardness comparison of paracetamol tablet made with BARETab® PH and physical mixing



Friability: Paracetamol tablet containing BARETab® PH pass in friability however physical mixing containing paracetamol tablet failed in friability test. Friability of both samples tablets mentioned in Table :3.

Disintegration time: Paracetamol tablet containing BARETab® PH has less disintegration time as comparative to physical mixing containing paracetamol. Average disintegration time mentioned in Table:3.

Fig:4 Disintegration time comparison of paracetamol tablet made with BARETab® PH and physical mixing

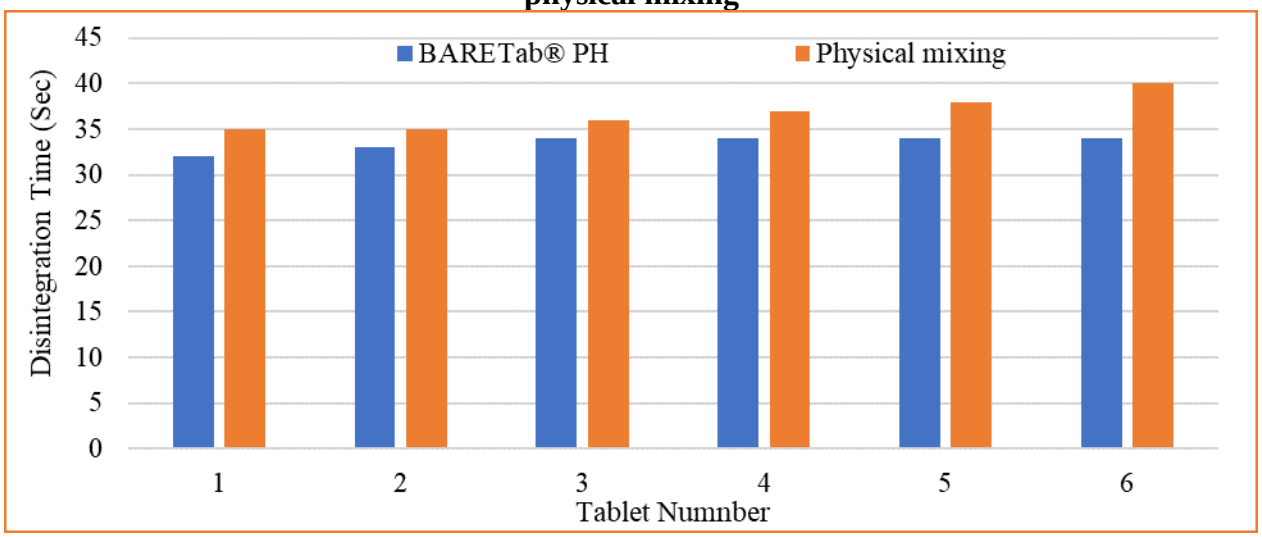
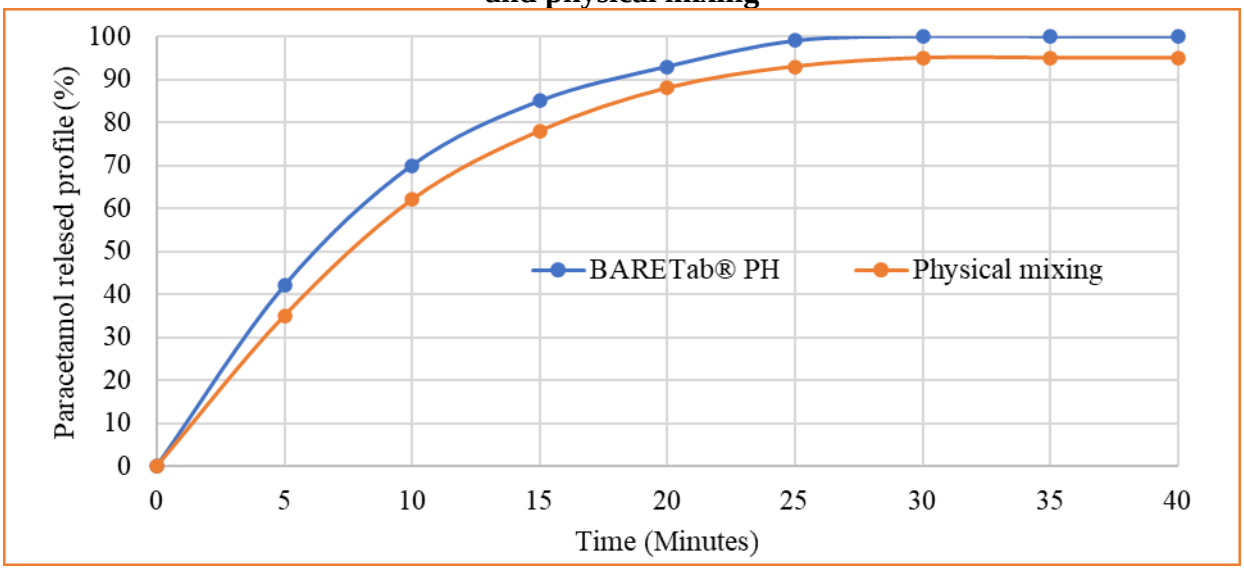


Table:3 Evaluation of paracetamol Tablet made with BARETab® PH and physical mixing

Characteristics	BARETab® PH	Physical mixing
Tablet appearance	White color, flat, round tablet and free from all visual defects	White color flat, round tablet and found sticking, capping, lamination and weight variation
Average tablet weight (mg)	900	857
Average thickness (mm)	5.5	5.5
Average hardness (N)	65.5	32.9
Friability (%)	0.098	1.20
Average disintegration time (Sec)	33.5	36.8

Dissolution profile: Paracetamol released fast from BARETab® PH containing tablet as comparative to physical mixing. Average paracetamol release profile of both tablet samples shown in Fig:5.

Fig: 5 Paracetamol released profile comparison in paracetamol tablet made by BARETab® PH and physical mixing



Conclusion: In this study, we have elucidated that BARETab® PH has multi-functional properties, its particles more homogeneous, larger surface area and more densities and compressibility which is improved paracetamol blend flowability and helps during tableting. BARETab® PH improved paracetamol tablet surface and all tablets were free from all defects. BARETab® PH provided higher tablet hardness, weight uniformity and lesser disintegration time, friability and fast drug released profile. Whereas physical blend containing paracetamol have very poor flowability and heterogeneous blending which shown unequal tablet machine die-cavity filing and caused more weight variation and unequal paracetamol distribution in the tablets and poor compressibility. It gave less tablet hardness, more friability, disintegration time, late and variation in paracetamol released form tablets and with tablet defects like sticking, laminations and capping.

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Conflicts of interests

The authors state and confirm no conflict of interests. No direct funding was received for this study.

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