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RESEARCH ARTICLE

MULTIFUNCTIONAL EXCIPIENTS PERFORMANCE EVALUATION INTO POOR WATER-SOLUBLE DRUGS HYDROCHLOROTHIAZIDE IN ORAL SOLID DOSAGE FORMS

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ABSTRACT

Multifunctional excipients are also called all-in-one excipients and are made using co-processing technology. Co-processing is a way to enhance individual excipient physical properties like bulk density, texture, particle size, flowability, and functionality like tablet hardness, weight uniformity, drug uniformity, disintegration, and dissolution profile. BARETab® SL is a multifunctional excipient made by using co-processing technology, and specially developed for poor water-soluble active ingredients, we have manufactured a Hydrochlorothiazide tablet using BARETab® SL and individual excipient, evaluated pre-compression and post-compression parameters parallelly evaluate multifunctional and individual excipient physical and morphological properties. Multifunctional excipients BARETab® SL have outstanding physical properties and tablet properties, it gives higher tablet hardness, lower disintegration time, and enhanced poor soluble API solubility.

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INTRODUCTION

An excipient plays an important role in manufacturing dosage forms. Oral Solid dosage forms are easy to manufacture and easy to handle and the patient complies (Elder, 2016). To manufacture OSD excipients are used 35% to 65% and all excipients should be non-reactive and give desired functional properties (Abrantes *et al*., 2016). The global pharma excipient market has shown significant growth in recent years because excipients are increasingly aiding APIs in achieving better functionality and overcoming solubility challenges by providing a product to competitive benefit. Various technologies have been introduced to improve the solubility through Physical changes by Particle size reduction, Polymorphism, Co-solvency, Co-crystallization, Hydrotropy, Micronization, pH alteration, change in the dielectric constant of the solvent, Changing into amorphous forms, and Slat formation (Monsuur, 2010). Chemical modifications using Surfactants, Complexation, Hydrates or solvates, Soluble pro-drugs, Selective adsorption on insoluble carriers, Functional polymer technology, Precipitation inhibitors, Solvent deposition, Ultrasonic waves, Spherical agglomeration, co-precipitation process and so on can be targeted to progress the bioavailability of poorly solvable molecules (Kanojia, 2013). Solubility, the phenomenon of dissolution of solute in solvent to give a homogeneous system, is one of the important parameters to achieve the desired concentration of drug in systemic circulation for a desired pharmacological response. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for generic development. Solubility is not to be confused with the ability to dissolve or liquefy a substance, since these processes may occur not only because of dissolution but also because of a chemical reaction. For example, zinc is insoluble in hydrochloric acid, but does dissolve in it by chemically reacting into zinc chloride and hydrogen, whereas zinc chloride is soluble in hydrochloric acid (Brahmankar, 2009). Solubility does not depend on particle size or other kinetic factors; given enough time, even large particles will eventually dissolve. More than approximately 40% of APIs developed in the pharmaceutical industry are practically insoluble in water. Solubility is a major challenge for the formulator [6]. Any drug to be absorbed must be present in the form of a solution at the site of absorption. Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include physical and chemical modifications of drugs and other methods like particle size reduction, crystal engineering, salt formation, solid dispersion, use of surfactant, and complexation, etc. The selection of solubility improving method depends on drug properties, site of absorption, and required dosage form characteristics (Saharan, 2009). There are many surfactants like ammonium lauryl sulfate, sodium lauryl sulfate, and the related alkyl-ether sulfates sodium lauryl sulfate also known as sodium lauryl ether sulfate (SLES), sodium myrethsulfate. Sodium stearate is used to enhance drug solubility [8]. Surfactants are added into the blend after lubrication and compress the tablet.But when mixing physically it may be a challenge due to its minimal quantity of use (Fiese, 1990). Now, many multifunctional excipients coming into the market, They contain all the required excipients like binders, glidants, disintegrants, surfactants, and lubricants. When mixing a small amount of ingredients in co-processing, the finished product becomes homogeneous (Gohel, 2005). BARETab® SL is a multifunctional co-processed excipient and has excellent flowability, wide range particle size distribution, and a wide range of bulk density. We have selected Hydrochlorothiazide to evaluate multifunctional excipients' functional performance. Because it is a poor water-soluble API (Sreekanth Babu, 2013).

In this study, we will study multifunctional excipient BARETab® SL and individual excipients performance evaluation in the poor soluble Pharmaceutical active ingredients Hydrochlorothiazide and evaluate the physical properties of both types of excipients, pre-compression, and post-compression study of Hydrochlorothiazide.

MATERIAL

BARETab® SL, Microcrystalline cellulose (HiCel 90M), Croscarmellose Sodium (HiLose) and Magnesium stearate (MagLub) manufactured at Sigachi Industries Ltd. Colloidal Silicon dioxide was purchased from a reputed manufacturer Wacker. Sodium Lauryl sulfate was purchased from Glenthan Life Science in the United Kingdom. Hydrochlorothiazide was purchased from "SIMSON Chemie, form Mumbai. Other chemicals are used AR grade in this study.

METHOD

Morphological study

Scanning Electron Microscopic: Take approximately 1 to 2 milligrams of sample and mounted it on double-sided taped-on aluminum stabs. Placed stabs into sample compartment into a microscope. Micrographs were taken at appropriate magnification and particle surface visualization was detailed and analyzed by a scanning electron microscope at SICART University, Anand, Gujarat (India).

Pre- Evaluation of BARETab® SL and Final Blend

Physical Parameters Evaluation of Individual Excipient

Untapped Density: Untapped bulk density analyzed by Scott volumeter. Weight the empty cup, place it under the chute and 10g of each sample is poured into a funnel through a volumeter, at a rate suitable to prevent clogging, until the cup overflows. Level the excess powder and weigh the filled cup (Monika, 2017).

$$\text{Untapped density (g/ml)} = \frac{\text{Sample Mass(g)}}{\text{Sample Volume(ml)}} \quad \text{.....(i)}$$

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 a fixed number of tapped (500) until the powder bed reaches a minimum volume (United States Pharmacopoeia, 2018).

$$\text{Tapped density (g/ml)} = \frac{\text{Sample Mass(g)}}{\text{Sample Volume(ml)}} \quad \text{.....(ii)}$$

Hausner's Ratio: It is an indirect index for ease of measuring powder flow. Lower Hausner's ratio (<1.25) indicates good flow property (USP, 2018).

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Untapped density}} \quad \text{.....(iii)}$$

Compressibility: Compressibility is known as Carr's index. Based on the apparent bulk density and the tapped density. Percentage compressibility is calculated by the below formula (United States Pharmacopoeia, 2018)

$$\text{Compressibility (\%)} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100 \quad \text{.....(iv)}$$

Angle of Repose: The angle of repose is the angle obtained between the free-standing surface of the powder heap and the horizontal plane. It was determined by using the fixed funnel method. 20 gm of final blend powder was poured into the funnel keeping the orifice of the funnel blocked by thumb. When the powder was cleared from the funnel then the peak height was measured (USP, 2018).

Particle Size Distribution Analysis: Particle size distribution was analyzed by using the dry dispersion method Aero S accessory (Malvern Mastersizer 3000 Instrument v3.81)**.**

API Blending Method and Tablet Manufacturing: Weigh the required quantity of the below-mentioned ingredients.

Table 1. Hydrochlorothiazide 25mg Tablet Manufacturing Formula

Ingredient Name	BARETab SL		Individual Excipient	
	mg/tab	w/w%	mg/tab	w/w%
Hydrochlorothiazide	25.00	25.00	25.00	25.00
BARETab® SL	75.00	75.00	-	-
HiCel MCC	-	-	69	69
HiLose	-	-	3.75	3.75
Colloidal silicon dioxide	-	-	1.5	1.5
MagLub	-	-	0.375	0.375
Sodium Lauryl Sulfate	-	-	0.375	0.375
Total	100 mg	100%	100 mg	100%

Blending Method

1. **Multifunctional Excipient**: Take the required quantity of API and BARETab SL into an octagonal blender and blend it for 10 to 15 minutes at 25 RPM [15].
2. **Individual Excipient**: Take the required quantity of HiCel MCC, HiLose, and transfer it into the octagonal blender, blend it for 5 minutes add API, and blend it for 5 minutes. Add colloidal silicon dioxide into previous blend and blend it for 5 minutes after that add Sodium lauryl sulfate and blend it for 5 to 6 minutes and at last add magnesium stearate and lubricate it for 3 minutes at 25 RPM.

Pre-Compression Parameter Evaluation: As per above mentioned method, evaluate the final blend Untapped density, Particle size, Carr's index, and Angle of Repose.

Physical appearance: The general appearance of Hydrochlorothiazide tablets was studied visually in shape, color, and texture.

Weight variation: Weight variation test was performed by weighing 10 tablets individually using a four-digit digital weighing balance (Mettler Toledo, MS304S/A01) and calculating the average weight (USP, 2018).

Hardness: Randomly 10 tablets were selected and analyzed by an electronic digital hardness tester machine (TH1050M). A single tablet was placed between two anvils, the 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 (United States Pharmacopoeia, 2018).

Friability: 10 tablets were taken and weighed by using an electronic digital balance which was considered as the initial weight. All the tablets were placed in the drum of the 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 general chapter, the tablets should not lose more than 1% of their total weight.

$$\text{Percentage Friability} = \frac{\text{Initial weight(gm)} - \text{Final weight(gm)}}{\text{Inital weight (gm)}} \times 100 \quad \text{(v)}$$

In-Vitro Disintegration Time: The disintegration time of Hydrochlorothiazide tablets was analyzed by using a tablet disintegration tester (Labindia, DT1000) at 37±2°C in 900 ml De-mineralized water. Six tablets were taken and one tablet was introduced in each tube, disk was placed and the basket was positioned in one liter beaker containing 37±2°C temperature of the

water. Note down tablet breaking time. Noted the time when the tablet broke down into smaller particles (2018).

In-Vitro Dissolution Profile: Hydrochlorothiazide tablet drug released profile was analyzed by using a dissolution test apparatus (Labindia, DS8000) and followed by USP method, apparatus no 1 (Basket), speed 100 rpm for 60 minutes in 900 ml of 0.1 N hydrochloric acid at 37±0.5°C medium temperature. Randomly select 6 tablets and one tablet introduced in each beaker of dissolution. 5 ml samples were withdrawn from each beaker at different time intervals 5, 15, 30, 45 and 60 minutes. Samples filter through What man filter paper (No. 42). Take 1 ml filtrate sample from the beaker and transfer it into 10 ml of volumetric flask and dilute up to 10 ml by using a dissolution medium. Repeat the same procedure for all remaining 5 tablets containing samples. Take standard and sample absorbance by using UV Visible SpectrophotometerUV-1900 (Shimadzu) at λ=272 nm wave length. Calculate the Hydrochlorothiazide drug released profile with the help of the below-mentioned formula [17].

Amount of Drug Released (mg) = Concentration of released drug × Dilution factor × Volume of dissolution medium / 1000

Drug Released (%) = Amount of drug released (mg) / label claim (mg) x 100 (vi)

RESULTS AND DISCUSSION

Scanning Electron Microscope Images: BARETab® SL is a co-processed product and each ingredient is mixed with co-processing. It each particle is spherical in shape which is shown in Fig: 1.

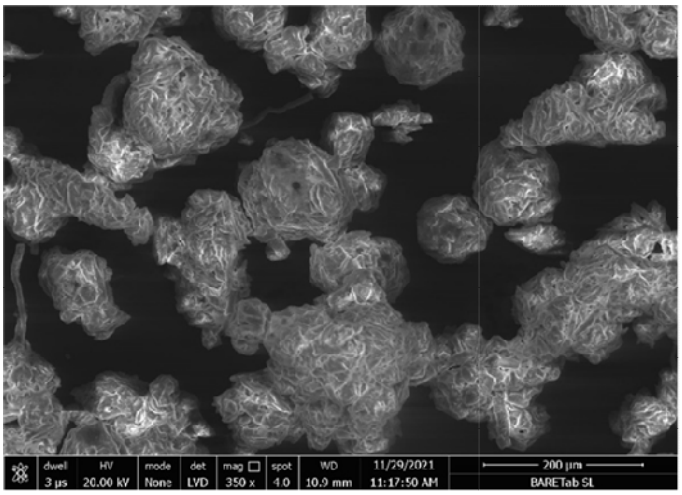

Figure 1. Scanning Electron Microscopic Image at 350x magnification of BARETab SL

Physical Parameters: BARETab® SL and Individual excipient blend physical parameters mentioned in table no 2.

Table 2. Multi-Functional Excipient BARETab® SL Physical Parameters

Parameters	BARETab® SL	Individual Excipient blend
Bulk Density (g/cc)	0.30	0.29
Tapped Density (g/ml)	0.41	0.43
Average Particle Size (µm)	125	102
H.Ratio	1.37	1.48
Carr's Index (%)	26.82	32.56
Angle of Repose (°)	35	42

Hydrochlorothiazide blend Pre-Compression Evaluation: Pre-Compression parameter's physical evaluation result is mentioned in Table 3.

Table 3. Pre-Compression Parameters Hydrochlorothiazide Tablet

Parameters	BARETab® SL	Individual Excipient blend
Bulk Density (g/cc)	0.37	0.34
Tapped Density (g/ml)	0.49	0.53
Carr's Index %	24.49	37.03
angle of Repose (°)	38	44
Pre-Compression Force (kN)	1.1	1.1
Main Compression Force (kN)	6.8	6.8
Tablet Mass (mg)	100	100

Tablet Compression: With BARETab® SL, a tablet compression machine ran smoothly and at a higher 25 RPM, with individual excipient blend, the tablet machine did not Run smoothy it ran under pressure, at high RPM tablets are rejected in weight variation so the machine run at slow speed 15 RPM.

Physical Appearance: All tablets are white in color with an 8.00 mm diameter and round shape, all tablets are physical tablet defect-free. But individual excipients containing few tablets were observed with defects.

Weight Variation: We have found weight uniformity in BARETab® SL containing Hydrochlorothiazide tablets, and found little weight variation with individual excipient blend but all tablet passed in limit. Average weight of both samples mentioned in Table 4.

Thickness: Tablet thickness is maintained at 2.95 mm and all tablet thickness between ± 0.2 mm and shown in table no 4.

Hardness: The hydrochlorothiazide tablet average hardness of both samples is mentioned in tablet:4.

Friability: Tablet friability results of both samples is under limit, and mentioned in Table 4.

In-Vitro Disintegration: Hydrochlorothiazide average disintegration time mentioned in Table 4.

In-Vitro Dissolution Profile or Drug Released Profile: Hydrochlorothiazide drug should be releasing more than 60% in 60 minutes as per United States Pharmacopeia (USP). The percentage of drug release profile is mentioned in Table 4.

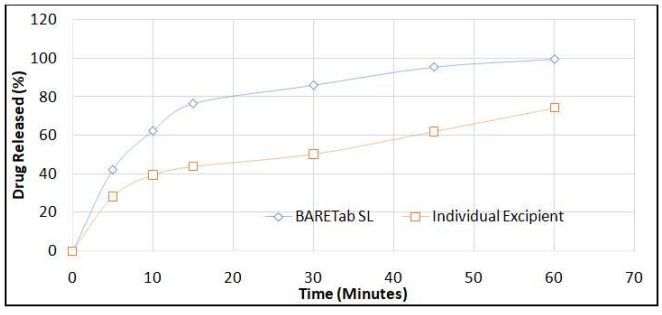

Figure 2. Hydrochlorothiazide Tablet Drug Released Profile with BARETab®SL

Table 4. Evaluation Parameters of Hydrochlorothiazide Tablet

Parameters	BARETab SL	Individual Excipient
Average Tablet Weight (mg)	100.0	100.2
Average Tablet Hardness (N)	133.9	98
Thickness(mm)	2.95	2.96
Diameter (mm)	8.00	8.00
Friability (%)	00	0.06
Disintegration Time (Min:Sec)	00:53.00	1:23:00
% Drug Release (60 min)	99.64	74.23

CONCLUSION

Multifunctional excipient BARETab SL Speciality is to enhance the solubility of poor water-soluble pharmaceutical active ingredients. In this study, we have successfully manufactured a Hydrochlorothiazide tablet using a multifunctional excipient and individual excipient. BARETab SL enhanced Hydrochlorothiazide tablet solubility, drugs are released 99.64% in 60 minutes, and individual excipient drug released profile 74.23%. Individual excipient contains sodium lauryl sulfate, but due to the small quantity, it is not mixed properly. As per United States Pharmacopoeia, Hydrochlorothiazide should be released more than 60% in 60 minutes. BARETab SL provides very good flowability and blending properties and it enhances tablet appearance, hardness, friability, and disintegration time as well as increases drug release of poorly water-soluble API.

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Conflict of Interest: The authors state and confirm no conflict of interest. No direct funding was received for this study.

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