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FULL PAPER

Evaluation of multifunctional co-processed excipient improvement of tableting performance

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The excipient industry has been associated with the food industry. The food excipients industry products have helped in maintaining high safety practices. The emphasis on purity, regulation, safety, and standards of excipients has led to the formation of an international sector. The International Pharmaceutical Excipients Council (IPEC), which is a triplicate council, has presentations from Europe, the United States, and Japan to synchronize standard requirements concerning purity and functional testing. A new multifunctional co-processed excipient is presented in this study. The aim is to develop and improve tableting performance and produce cost-effective tablet dosage forms. For this study, three compendia excipients were selected as traditionally most frequently used excipients filler /carriers, combined with different proportions, which might lead to the formulation of a new product having better properties compared to the simple physical mixing of the component. Macrolose were prepared with varying percentages of the three excipients (microcrystalline cellulose, lactose monohydrate, and sodium starch glycolate) to evaluate the effect of the optimized new co-processed excipient on the stability and physical properties of the final granulation mixture and the manufactured tablets.

KEYWORDS

Co-processed excipient; tablet formulation; direct compression; tableting performance.

Introduction

Dosage forms of pharmaceutical substances contain pharmacologically active compounds and excipient additives to support the formulation and manufacturing for patient administration. The final dosage form specification, particularly regarding stability and bioavailability, depends on the choice of excipients, their concentrations, and interactions with the active compound and between each other [1]. An excipient of inactive substances is preferable which can be used as a carrier for the medication's active ingredients. Moreover, excipients can be used to facilitate the manufacturing process [2]. The International Pharmaceutical Excipients Council (IPEC) has defined excipients as "inactive vehicle medium substance that serve for a drug or other active substance which is safe and intentionally formulated with the system of drug delivery". Excipients, for

example, can (a) aid in drug delivery processing during the manufacturing process; (b) support, protect, and stability-enhancing, bio-availability and also acceptable by the patient; (c) Product identification assisting; and (e) Further attributed enhancement of effectiveness, safety, or drug delivery of the shelf life and during use [3]. The excipients industry is an extension of the food industry [4,5]. Excipients have recently been considered inactive ingredients. pharmaceutical scientists, with time, consider that excipients are not inactive. They frequently show a significant impact on the manufacturing process in aspects of safety, quality, and efficacy of the drug substances of the dosage form. The performance variability of excipients shows an impact on the batch-to-batch within a single manufacturing process and manufacturers and also between several batches of different manufacturers arises an understood as a key determinant of dosage form performance [6]. The medicine dosage form, regardless of the composition or mode of use, should comply with the following requirements that underpin safety, efficacy, and quality; (a) contain an accurate dose; (b) be taken or administered conveniently; (c) the drug may in a form for absorption or other delivery way to the target; (d) remain same quality during shelf-life and period of usage; and (e) manufacturing process does not compromise performance and is reproducible and economically acceptable [7]. Tablet manufacturing was changed by two introductions, the direct-compression process with high-speed machining. Both of these developments increase demand for the excipient's functionality in terms of flow and compression properties. Solid handling engineering of individual excipients and combinations excipients using co-processing by several kinds of particle modifications need to provide an attractive tool for the development of high-functionality excipients which are fit with modern tablet manufacturing processes [8]. Most formulations contain a higher content of excipients compared to the active ingredient as a consequence the excipients may play a major role in controlling the formulation's functionality and processability [9]. The ideal method of tablet manufacturing is the compression process [10]. A comprehensive study in this work addressed an issue of excipients with their interaction with active ingredients in pharmaceutical industries which is not been well reported in the literature previously.

Experimental

Hypothesis and objectives

The main objective of this work is a new excipient development associated with excipient co-processing and a novel excipient. A full study of the physical properties of newly prepared excipients in the aspect of formulation, stability, particle size, and mixing efficiency to lead to reduction of the manufacturing process.

Development of new excipient

The development of new excipients does not show much activity as observed over the recent years, not even a single excipient material was introduced to the market [11]. The main reason is attributed to the high cost involved in excipients discovery and development. An increasing number of new drug moieties with varying physicochemical and stability properties led to growing pressure on formulators to find new excipients that can achieve well-desired functionalities [12]. A new excipients mixture through co-processing of two or more existing excipients is coming into the market without undergoing the rigorous safety testing of completely new chemicals. This method is interesting due to the products being modified physically in several ways without altering the chemical structure [13]. The co-processing is intensively explored for the direct preparation

of compressible adjuvants due to its cost-effectiveness and can be prepared in-house upon the functionality requirement. The present work is focused on the properties of the co-processed compressible adjuvants which are available in the market [14]. The present usage of term "direct compression" is used to refer to the process by which tablets are compressed directly from powder blends of active ingredients and suitable excipients. No pre-treatment for powder blends using wet or dry granulation is involved [15]. Co-processing is attractive because the products are physically modified especially without altering the chemical structure. A fixed and homogenous component for the formulation can be achieved by embedding them within the fine powder. Segregation is diminished due to the adhesion of the actives on the porous particles making the process validation and in-process control easy and reliable [16]. A co-processed excipient is a mixture containing more than one excipient and not prepared by simple physical mixing. These materials are formulated with co-grinding, co-crystallization, co-precipitation, spray drying, and common solvent evaporation. The physical properties namely size, shape, and density of particles, may differ from one excipient to another resulting in segregation and non-uniformity [17]. Solid oral dosage forms, namely tablets and capsules, are the most common form of drug product of pharmaceutical manufacture [18]. Tablets and capsules contain the API and excipients. The excipients play several roles including fillers, binders, disintegrates, glidants, and lubricants [19]. The tablet formulation involves several components, each of which is present to facilitate the manufacture or to control the biological performance of the dosage form [20].

Method

The materials used in this study were divided into two types, the active pharmaceutical ingredient (APIs) which is a part of the pharmaceutical dosage form that produces the intended effects, and the inactive ingredients (excipients) which are any component of the pharmaceutical medication other than the active ingredient.

Active pharmaceutical ingredient

The active substances in the study were selected so that their concentrations vary in dosage form, from low concentrations that do not exceed 5%, such as bisoprolol, to high concentrations exceeding 70%, such as ciprofloxacin. The active ingredient for the formulation is listed in Table 1.

TABLE 1 Active ingredients used in trials

material	specification
Meloxicam	USP
Atenolol	BP
Norfloxacin	USP
Levocetirizine	IH
Sildenafil Citrate	IH
Folic Acid	BP
Ranitidine HCL	USP
Atorvastatin Calcium	USP
Bisoprolol fumarate	USP

Inactive ingredients

The adjuvants were selected from among the available, inexpensive and multi-use materials in the pharmaceutical industry. These materials are either used in the formula of co-processed excipient, or the preparation of the new excipient but not used in the formula where the use of purified water and ethanol, or used to add the step of compression in case of low flowability of some high concentrated dosage forms (e.g., magnesium stearate as a lubricant), The inactive ingredients for this formulation is presented in Table 2.

TABLE 2 Inactive used ingredients and solvents

Material	Specification	Manufacturer	Origin
Microcrystalline Cellulose 102	Eur, BP, JP, and NF	FMC	Ireland
Lactose Monohydrate	USP	DFE Pharma	Netherland
Maize Starch	USP and BP	Colorcon	Germany
Povidone K30	USP	Zhongbao Chemicals	China
Sodium Starch Glycolate	Eur-NF-JP	JRS Pharma	Germany
Croscarmellose Sodium	Eur-NF-JP	JRS Pharma	Germany
Magnesium Stearate	Eur, BP, JP, NF, and FCC	Merck	Germany
Ethanol	BP	Sudanese distillation	Sudan
Purified water	BP	Azal Pharma	Sudan

Method of preparation of co-processed excipients

For each preparation run, the following wet granulation steps were followed: *The weighing*: each material was weighed in a clean polyethylene bag using a calibrated digital balance. *Mixing*: Each material was added to a clean Polyethylene bag and the powder mixture was mixed manually for 5 minutes. *Wet massing*: The powder mixture was put in a stainless steel drum and the granulation liquid (purified water or ethanol) was added gradually and was stirred by using a glass rod till distinct granules were formed and the fine powder disappeared. *Granulation:* The wet mass was granulated by using a sieve size of 2 mm, and batch was passed through the sieve.

drying

The formulation prepared using purified water was dried for 24 hours at 50 °C using a conventional oven as a dryer, whereas the formulation prepared by using ethanol 96% was dried for 8 hours at 50°C using a conventional oven as a dryer. *Sizing*: The granulation was sized to the required size by using the suitable sieve; all dried granules were passed through sieve No. 25 (0.71 mm).

Preparation of co-processed excipients

The preparation of co-processed excipients was according to the formulations listed in Table 3. A different macro close concentration was prepared and presented in Table 4.

TABLE 3 Different macrolose preparations

No.	B# No.	Material used	Weight in grams	Remarks
		Microcrystalline cellulose 102	90	90%
1.	CL-1	Lactose monohydrate	10	10%
		Purified water	qs	
		Microcrystalline cellulose 102	70	70%
2.	CL-2	Lactose monohydrate	30	30%
		Purified water	qs	
		Microcrystalline cellulose 102	50	50%
3.	CL-3	Lactose monohydrate	50	50%
		Purified water	qs	
		Microcrystalline cellulose 102	30	30%
4.	CL-4	Lactose monohydrate	70	70%
		Purified water	qs	
		Microcrystalline cellulose 102	10	10%
5.	CL-5	Lactose monohydrate	90	90%
		Purified water	qs	
		Microcrystalline cellulose 102	12.5	25%
6.	CL-6	Lactose monohydrate	37.5	75%
		Purified water	qs	
		Microcrystalline cellulose 102	13.75	27.5%
7.	CL-7	Lactose monohydrate	36.24	72.5%
		Purified water	qs	
		Microcrystalline cellulose 102	15	30%
8.	CL-8	Lactose monohydrate	35	70%
		Purified water	qs	
		Microcrystalline cellulose 102	16.25	32.5%
9.	CL-9	Lactose monohydrate	33.75	67.5%
		Purified water	qs	
		Microcrystalline cellulose 102	17.5	35%
10.	CL-10	Lactose monohydrate	32.5	65%
		Purified water	qs	

TABLE 4 Different macrolose preparations with disintegrate

No.	B# No.	Materials used	Weight in grams	Remarks
		Microcrystalline cellulose 102	12.5	25%
		Lactose monohydrate	35.5	71%
1.	CL-11	Sodium starch glycolate	2	4%
		Purified water	Qs	
		Microcrystalline cellulose 102	25	50%
		Lactose monohydrate	23	46%
2.	CL-12	Sodium starch glycolate	2	4%
		Purified water	Qs	
		Microcrystalline cellulose 102	25	50%
3.		Lactose monohydrate	23	46%
	CL-13	Sodium starch glycolate	2	4%
		Ethanol 96%	Qs	
		Microcrystalline cellulose 102	25	50%
		Lactose monohydrate	23	46%
4.	CL-14	croscarmellose sodium	2	4%
		Purified water	Qs	
		Microcrystalline cellulose 102	25	50%
5.	CL-15	Lactose monohydrate	23	46%
		Sodium starch glycolate	2	4%
		Purified water	Qs	
		Microcrystalline cellulose 102	125	50%
6.	CL-16	Lactose monohydrate	115	46%
		Sodium starch glycolate	10	4%
		Purified water	Qs	

Evaluation of the co-processed excipients

Evaluation of co-processed excipient was according to the following standard methods, namely compressibility; followability by Hausner ratio and compressibility index; granule size; and moisture content, as depicted Figure 2.

Tablet preparation using the co-processed excipient

Direct compression method was used as per the steps of, weighing: Each material was weighed in a clean polyethylene bag alone using a digitally calibrated balance, *Mixing*: The materials were added to a clean Polyethylene bag and the powder mixture was mixed manually for 5 minutes, *Compression*: The formulation was compressed using the specified punch, weight and hardness were controlled as the required specification.

Tablets prepared from different macrolose preparations

Batches (150 tablets /batch) of meloxicam 15 mg tablets were prepared with different combinations of macrolose, CL-1 to CL-16 and 0.5% of magnesium stearate as lubricant. The only variable in the batches was the type of macrolose.

Active substances formulated with macrolose

Macrolose co-processed excipient was compressed alone as a placebo and with different drug substances with different strengths and physicochemical proportions, as summrized in Table 5.

TABLE 5 Active substances formulated with macrolose

No.	Drug Substance	Materials used in the formula	Unit formula Mg/tablet	Batch formula gms/batch	%	Tablet shape
1.		Folic acid BP	5.5	0.825		7.25 mm
	Folic acid 5 mg	Macrolose CL 12	143.5	21.525	95.67%	round
		Mag-sterate	1	0.15	0.667%	
		Atenolol	100	10	25%	11 mm round
2.	Atenolol 100 mg	Macrolose Cl-16	298	29.8	74.5%	
		Mag-sterate	2	0.2	5%	
		Raritedine Hcl	167.4	16.7	55.7%	9.7 mm round
3.	Raritedine 150	Macrolose Cl-16	131.5	13.15	43.7%	
	mg	Mag-sterate	1.5	0.15	0.5%	
		Atorvastatine	21.9	4.38	12.1%	8.6 mm round
4.	Atorvastatine 20	Macrolose Cl-16	157.2	31.44	87.4%	
	mg	Mag-sterate	0.9	0.18	0.5%	
		Sildenafil citrate	70.3	7.03	29.5%	Diamond
5.	Sildenafil 5 mg	Macrolose Cl-16	178.45	17.845	70%	Shape
		Mag-sterate	1.25	0.125	0.35%	
		Bisoprolol	10	2	5.9%	Heart Shape
6.	Bisoprolol 10 mg	fumarate	159.15	31.83	93.6%	
		Macrolose Cl-16	085	0.17	0.5%	
		Mag-sterate				
		Norfloxacin	400	40	57.14%	Caplet
7.	Norfloxacin 400	Macrolose Cl-16	196.5	29.65	42.36%	shape
	mg	Mag-sterate	0.35	0.35	0.5%	
		Levocetrizine	5	1	4.17%	7.25 round
8.	Levocetrizine 5	Macrolose Cl-16	114.4	22.8	95.33%	
	mg	Mag-sterate	0.0	0.18	0.5%	
9	Meloxicam 15 mg	Meloxicam	15	2.25	7.5	8.6 mm round
		Macrolose CL-16	184	27.6	92%	
		Magnesium Stearate	1	0.15	0.5%	
10	Placebo	Macrolose CL-16	200	20	100	8.6 mm round

Evaluation of tablets

To evaluate the functionality of the co-processed excipient, tablets were formulated from the active material and co-processed excipient. Randomly selected tablets were subjected to physical tests such as weight variation, hardness test, friability test, disintegration test, and thickness test according to USP 2010 [21,22].

Method for evaluation of macrolose

The macrolose powder was taken and specified visually to describe the powder. The moisture content of each batch was tested. The powder of each batch was prepared for compression with Meloxicam as per the formula in Table 4. The parameter of Meloxicam 15 mg was prepared and the specification of the formula is listed in Table 6.

TABLE 6 Formulation of meloxicam 15 mg prepared with macrolose

No.	Material	Wt/Unit /mg	Total Wt/ 150 Tabs/ g	Remarks
1	Meloxicam	15	2.25	7.5%
2	Macrolose	184	27.6	92%
3	Magnesium Stearate	1	0.15	0.5%
Total		200	30	

The compressed tablets were tested to evaluate macrolose with the tests of weight variation, hardness test, friability, disintegration and thickness of the tablet, as provided in Table 7.

TABLE 7 Meloxicam tablets prepared with macrolose

Batch No.	Mean Weight/mg	Hardness /Kp	Disintegration /min	Friability /%
CL-1	199.3	10.6-12.1	13:55	0.1
CL-2	203.6	9.5-13.9	20:30	0.081
CL-3	201.7	9.0-9.8	6:41	0.085
CL-4	199	7.3-8.0	3:50	0.13
CL-5	203.4	6.2-7.5	5:15	0.44
CL-6	202.8	5.9-9	7:15	0.23
CL-7	196.9	5.8-8.4	8:00	0.16
CL-8	203.1	6.2-8.8	7:43	0.18
CL-9	202.2	8.0-8.6	8:10	0.10
CL-10	198.7	6.1-8.3	8:15	0.28
CL-11	200.5	4.2-5.7	3:43	0.343
CL-12	203.6	6.3-9.0	2:51	0.175
CL-13	205.3	7.9-8.5	1:36	0.226
CL-14	201.8	7.1-8.9	4:30	0.3
CL-15	197.5	6.8-8.4	3:30	0.17
CL-16-II	200.2	7.4-9.2	2:44	0.199
CL-16-III	202.2	7.6-10.4	2:51	0.20
CL-16-IV	200.8	7.1-10.8	2:40	0.15
Specifications	200mg±7.5%	NLT 3 Kp	NMT 15 min	NMT1%

Stability conditions and packaging

An accelerated stability study was carried out at a temperature of 40±2 ^{o}C and Relative Humidity of 75%±5%. The samples were tested for 6 months. The real-time stability study was carried out at a temperature 30±2 ^{o}C and Relative Humidity of 65%± 5%. The samples were tested at the 3rd and 6th month of stability. The samples were packed primarily in transparent polyethylene bags. The secondary packs were white, high-density polyethylene (HDPE) plastic containers, of microlose density, as displayed in Figure 1. The physical test involving several basic parameters was conducted and the result is listed in Table 8.

TABLE 8 Physical tests of macrolose B# CL-16- II, III, and IV

Test	CL-16-II	CL-16-III	CL-16-IV
Weight(W) of sample	50 g	50 g	50 g
Bulk volume (V_0)	129 mL	133 mL	134 mL
Tapped volume (Vt)	107 mL	111 mL	110 mL
Bulk Density (D_b)	0.388 g/mL	0.376 g/mL	0.373 g/mL
Tap Density (D_t)	0.467 g/mL	0.450 g/mL	0.455 g/mL
Compressibility Index% (I)	17.05	16.54	17.91
Hausner ratio	1.206	1.198	1.22
Moisture content	5.7%	5.71%	5.6 %

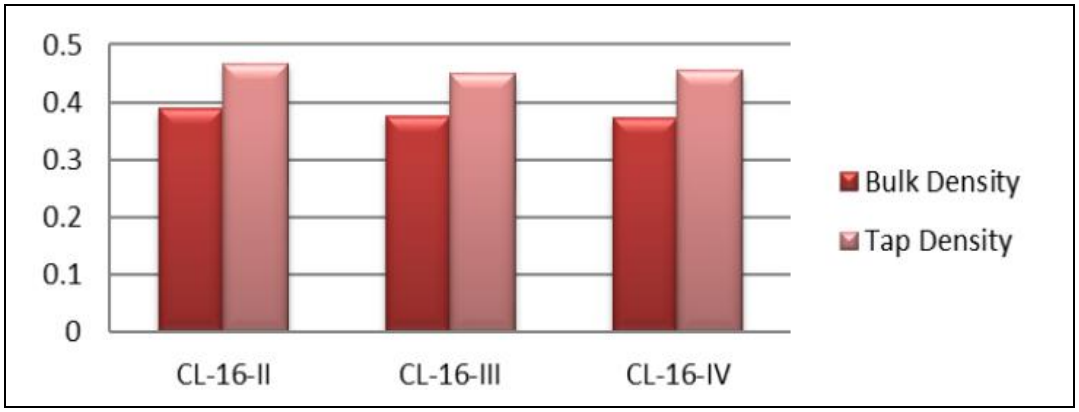

FIGURE 1 Macrolose density

Particle size analysis of macrolose

Macrolose CL-16 particle sizes were determined using sieves in deferment mesh, as indicated in Table 9 and Figure 3. Particle size distribution is presented in Figure 4.

TABLE 9 Particle size analysis of macrolose CL-16

Sieve No.	Particle size	Mid-Point	Weight/ g	%	Cumulative %
25	0.710-1.00 mm	0.855 mm	0.20	0.4	100.00
35	0.500 -0.710 mm	0.605 mm	11.87	23.74	99.6
60	0.250 -0.500 mm	0.375 mm	18.91	37.82	75.86
120	0.125 -0.250 mm	0.1875 mm	11.13	22.26	38.04
200	0.0630.125 mm	0.094 mm	5.11	10.22	15.78
Pass through #200	0.00-0.063 mm	0.0315 mm	2.78	5.56	5.56
Total			50.00	100%	100%

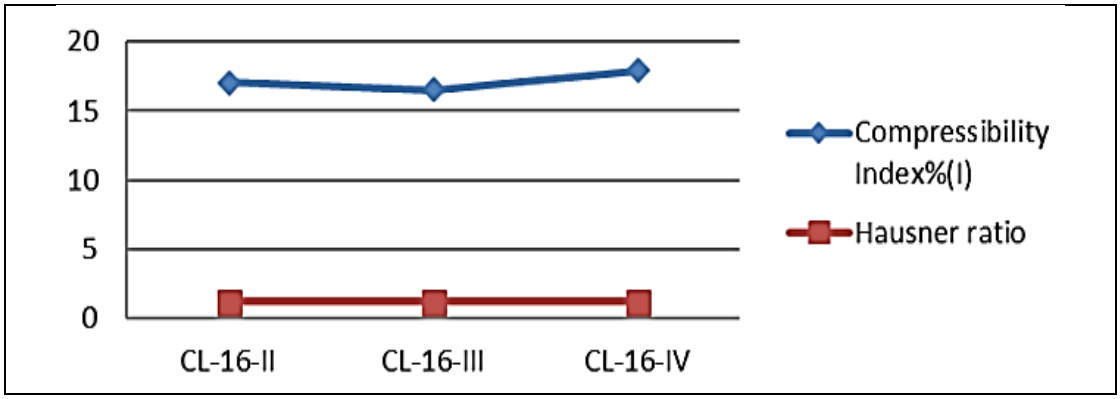

FIGURE 2 Compressibility index % (I) and Hausner ratio of macrolose

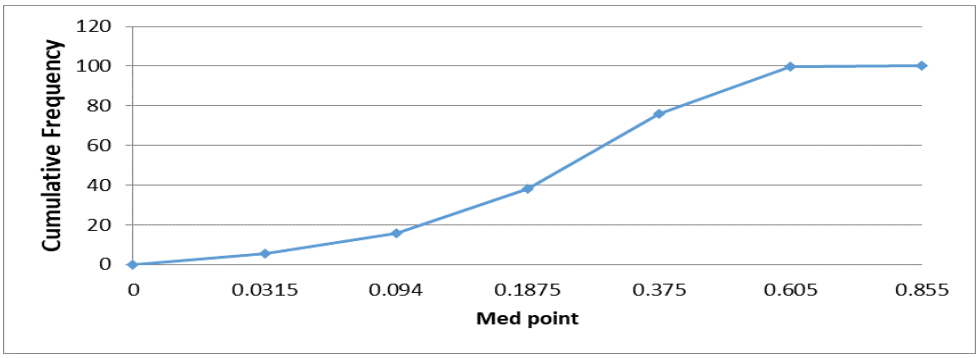

FIGURE 3 Particle size analysis of macrolose CL-16-II cumulative frequency

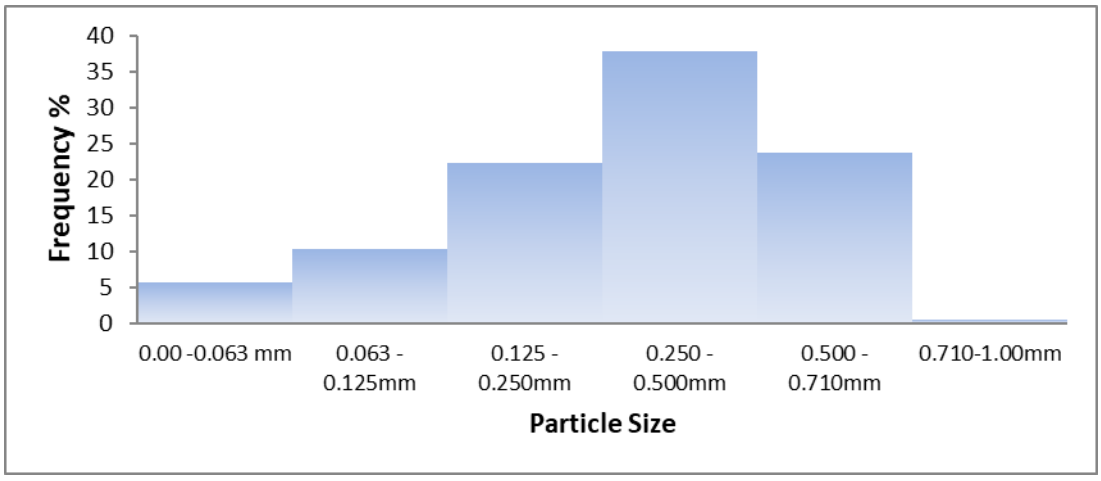

FIGURE 4 Distribution of particle diameters of macrolose CL-16-IIF

Macrolose was a combination of Lactose monohydrate and Microcrystalline Cellulose (MCC). To ensure good mixing and better control of particle size, the method of preparation was wet granulation. The combination of MCC and lactose gave a good formulation as DC filler for tablet compression, so meloxicam tablets were compressed by using Macrolose batches CL-1 to CL-5 and passed the appearance, hardness and friability tests, as presented in Table 3. Tablets were physically evaluated and Cl-4 was taken as the best formulation. CL-4 was further optimized (CL- 6 – CL-10). All formulations showed

variation in disintegration time. When 4% sodium starch glycolate was added (CL-11) the resultant tablets were lower in hardness and more friable, Table 4. A new formulation was prepared by taking CL-3 as a base formula and 4% sodium starch glycolate was added (CL-12). The tablets produced complied with the compendia specifications. Based on the above experiments, CL-12 was taken as the best-optimized co-processed excipient. A large batch of the same formulation was prepared (CL-16-I) from which, eight different active pharmaceutical ingredients of different strengths were prepared by the DC method. The produced tablets showed a very high dilution potential of the new excipient macrolose (57%), as indicated in Table 5. The evaluation of different tablets prepared was by BP2011 and USP 2010 requirements. For the stability study, all the QC parameters were within the limits from zero time up to 6 months of accelerated and real-time stability studies.

Conclusion

To sum up, the new co-processed excipient, macrolose, has successfully met most of the study's objectives and has demonstrated superiority over existing excipients. The active pharmaceutical ingredients used in Tables 4 and 5 ranged from 5 mg to 400 mg, which showed the high dilution potential of macrolose which reached 57%, while the best dilution factor of DC materials is 25%. The QC results demonstrated that the new co-processed excipient macrolose is useful DC multifunctional filler for producing cost-effective, safe and effective pharmaceutical products.

Recommendation

• Macrolose should undergo further advanced studies, including a full stability study, compressibility tests, and all physical tests with various active ingredients. In addition, large-scale batches should be prepared to assess its production feasibility for multiple types of drugs.

• Commercial production of macrolose for producing cost-effective drug products is recommended.

• Further studies is suggested on macrolose with different particle sizes and moisture content are recommended.

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Conflicts of Interest

All authors declare that there is no conflicts of interest in this article.

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