Journal of Advanced Drug Delivery (JADD)
Volume 1, Issue 6, December -2014

ISSN NO: 2348-3278

ISRA IMPACT FACTOR: 0.46

Over View of Co Processed Excipients Used To Improve Tabletting Performance

Uma Rani. G *, Naheed Begum

ABSTRACT: Tablets are the most preferred dosage form of pharmaceutical professionals because they can be accurately dosed and provide good patient compliance. The ease of manufacturing, convenience in administration, accurate dosing, and stability compared to oral liquids, tamper proofness compared to capsules, Safe compared to parental dosage forms makes it a popular and versatile dosage form and can be produced at a relatively low cost. Tablet manufacturing techniques have undergone rapid change and development over last decades with the emergence of novel excipients, to justify the high rise in new drug development and high industrial output demand .new combinations of existing excipients are an interesting option for improving excipient functionality and to improve the tabletting performance. This in turn has lead to an increased research and detailed study for developing newer excipients by co processing technique which will improve the tablet manufacturing process. This review highlights the various co processed excipients which will be used to improve the tabletting performance.

Keywords: Excipients, Co-processing, Co-processed excipients, Functionality.

INTRODUCTION

A co-processed excipient is a combination of two or more compendia or non-compendia excipients designed to physically modify their properties in a manner not achievable by simple physical mixing, and without significant chemical change. Co-processing offers many advantages such as improvising flow properties by controlled optimal particle size and particle-size distribution, compressibility, dilution potential, fill weight variation, flow properties, lubricant sensitivity.[1] It can also improve the tablet hardness and decreases the disintegration time. The actual process of developing a co-processed excipient involves following steps such as identifying the group of excipients to be co-processed by studying the material characteristics and functionality requirements, selecting the proportions of various excipients assessing the particle size required for co-processing, selecting a suitable process of drying and optimizing the process. [2]

RECENT RESEARCH WORK DONE ON COPROCESSED EXCIPIENTS[17,18,20]

Uma Rani.G , Asst. Professor, Department of Pharmaceutics at RBVRR Women's college of Pharmacy, Affiliated to Osmania University, Hyderabad

Co processing of lactose: In solid dosage forms, lactose is probably the oldest but still one of the most important diluents in tabletting. However, the inadequate compactibility and poor flow properties of lactose monohydrate powder limits the use of crystalline a -lactose monohydrate as a filler-binder for direct tabletting. Many researchers and excipient manufacturers modified crystalline a -lactose monohydrate to achieve a product exhibiting good compactibility, reduced capping tendency and good flow properties to meet the need of excipients for direct compression excipients .

Processing of lactose into small α-lactose monohydrate agglomerates (e.g., Tablettose, Pharmatose DCL 15) or spray-dried lactose was performed to improve its direct tabletting characteristics. This processed lactose has better fluidity and compactibility than regular lactose. However, the compressibility of spray-dried lactose is borderline, and furthermore, it has relatively poor dilution potential. As spray-dried lactose loses compressibility on initial compaction, it does not lend itself to rework. Later on, binary mixtures of crystalline a -lactose monohydrate with MCC, povidone or starch have been tried but it only results in increase of the compressibility of the mixtures but no improvement in flow ability as compared with pure a -lactose monohydrate .Hence, efforts were made towards the development of co processed lactose[7/8].

Co processing of 93.4% a -lactose monohydrate with 3.2% povidone and 3.4% crospovidone resulted in Ludipress (BASF AG, Ludwigshafen, Germany), which is a suitable filler for direct tabletting on high speed presses. It is odorless, tasteless, white free-flowing granules especially developed for direct compression, but is also suitable as filler for hard gelatin capsules. Formation of polyvinyl pyrrolidone and crospovidone coat over lactose powder imparted excellent flowability and low degree of hygroscopicity to the lactose. Moreover, hardness of the tablets produced is also independent of machine speed. The binding properties of Ludipress, both unlubricated and lubricated with 1% magnesium stearate, are good and were found to be much better than those of the physical mixture although Ludipress contains a disintegrant, the disintegration of tablets takes longer than tablets containing a-lactose monohydrate, anhydrous ß -lactose, spray-dried lactose or Tablettose[9]. The length of disintegrating time is attributed to the presence of polyvinylpyrrolidone. Ashrafi et *al.* reported that Ludipress, when used in high amount, can extend the sustaining effect of the formulation to some extent.

Ludipress[10,11,12] exhibited better flow rate compared to Avicel PH 101 and has the highest flowability among various lactose based directly compressible excipients (Cellactose, Tablettose, Fla flo lactose) as inferred from its lower static and dynamic angle of repose than other excipients. Determination of tablet disintegration time revealed a disintegration time minimum at about 100 MPa for Ludipress compacts. Tablet disintegration time of Ludipress based compacts were not influenced at above 100 MPa compaction pressure whereas Cellactose [7] showed a significant increase in disintegration time (> 20 min) at compaction pressures above 100 MPa. The ability to form coherent compacts of Ludipress was similar to Cellactose and Avicel PH 200, whereas tablets made from the physical mixture resulted as significantly softer. At a compaction pressure of 100 MPa, friability of Ludipress compacts was ~ 0.2%. To obtain similar values for tablets prepared with Tablettose, compaction load of 200 MPwas necessary. Authors have also concluded that in terms of a multipurpose-excipient, Ludipress should be given preference in the formulation of low dosed drugs as Ludipress based tablets exhibited optimum disintegration time and compression pressure independent dissolution of glibenclamide. However in one study, Baykara et *al.* reported that Ludipress has stable flow properties but its dilution potential with Acetaminophen is lower than Avicel PH 101, Elcema G250 or Elcema P050.

Schmidt and Rubensdorfer evaluated the powder and tabletting properties of Ludipress and found that Ludipress[8] samples exhibited a good batch-to-batch uniformity and flow characteristics compared with the physical blends and other excipients investigated. Moreover, Ludipress has the ability to form coherent compacts similar to Cellactose and Avicel PH 200, whereas tablets made from the physical blend resulted as significantly softer[15,16,]. Heinz et *al.* found that the tensile strength of tablets made of Ludipress increased linearly with compaction pressures up to 300 MPa and independent of the geometry of the tablets (diameter, thickness, shape). It was found that the tensile strength of tablets made of Ludipress increased linearly with compaction pressures up to 300 MPa, which was independent of the geometry of the tablets. The equation can be derived to correlate compaction pressure and hardness of the tablet and with slight modification for scale-up from a single-punch press to a rotary tabletting machine. Tablets produced in the rotary machine at the same pressure have a slightly higher tensile strength. The rate of increase in pressure and, therefore, the throughput, has no effect on the tensile strength of Ludipress tablets. It is thought that a certain minimum dwell time is responsible for this difference. They concluded that the production of tablets based on Ludipress can be scaled up from one rotary press to another without problem if the powder mixtures are prepared with the same mixing energy .[10]

Cellactose: Cellactose is a co-processed product consisting a-lactose monohydrate (75%) and cellulose (25%). Coarse and regular grade sieved crystalline fractions of lactose monohydrate have good flow properties but lack compressibility. Co processing of crystalline a –lactose monohydrate with powdered cellulose (Cellactose, Meggle) or MCC (Microcell, Meggle) has resulted in improved bonding ability and excellent flow properties .

Cellactose was designed especially for direct tabletting combined filling and binding properties of the lactose and cellulose provides better tabletting performance at lower cost. It has excellent flowability attributed to its regular particle shape and favorable particle size distribution. Improved compactibility of Cellactose is owing to the principle consolidation mechanism of plastic deformation of cellulose and fragmentation of lactose. Moreover, Cellactose is shown to have a higher dilution potential than a physical mixture of its constituent excipient. The presence of cellulose fibers in the macro porous particles provides good disintegration properties to Cellactose. The moisture sorption of

Cellactose is much lower than that of cellulose alone as it is covered with lactose. Belda and Meilck found that Cellactose exhibited improved compactibility but impeded compressibility as compared to powder mixtures, each containing 25% (w/w) of Avicel PH101 or Elcema P100 and 75% Tablettose ® or lactose (100 mesh) . Arida and Al-Tabakha have found that tablet strength of Cellactose was higher than their physical mixture with same ratio. Improved tablet strength with Cellactose was attributed to the enhanced interparticle bonding in this co processed excipient. Reduction of interparticle bonding by the presence of a lubricant film on the particles and the relaxation of lubricated tablets is higher than that of unlubricated tablets in which interparticle attractions are large. However, the negative effect of magnesium stearate (lubricant) on interparticle bonding of Cellactose particles is smaller than the Physical mixture particles[20,23].

Jogani and Gohel Prepared lactose and MCC (3:1) base, and co processed directly compressible adjuvant using melt granulation technique using 12.5% of the polymer blend containing 1:9 ratio of PVP:PEG as meltable binder. The prepared agglomerates were evaluated for percentage fines and Carr's index and tablets were evaluated for tensile strength, friability and disintegration time. The authors concluded that melt granulation technique can successfully replace the classical wet granulation and spray-drying for the development of multifunctional directly compressible adjuvant for use in pharmaceuticals [10, 11]

Microcelac 100: Microcelac 100[15] is another marketed spray-dried product, containing a lactose monohydrate (75%) and MCC (25%). Microcelac with both filling properties of lactose and binding capacity of MCC provides better tabletting performance at lower cost. Muzíková and Zvolánková found that the tablet strength from pure Cellactose 80 was lower than that of those from MicroceLac 100 both without and with the lubricant in the compression forces of 6 and 8 kN. Disintegration time of the tablets from Cellactose 80 was longer than those from MicroceLac 100, except the tabletting materials containing 0.4% sodium stearylfumarate (Pruv) with a compression force of 6 kN. Michoel et *al.* Showed that Microcelac 100 has superior flow and binding properties and do not get influenced even on addition of folic acid. These improved characteristics are attributed to spray-drying. [(9, 10)]

Starlac: The latest material on the market is Starlac, a co processed filler-binder consisting of 85% a -lactose monohydrate and 15% native corn starch. Starch is a bi functional excipient, used as binder and disintegrant; however, it exhibits the lowest elastic recovery at high binding capacity. When starch is co processed with a -lactose monohydrate, it resulted in a product with excellent compactibility. The volume–pressure deformation properties of StarLac were found to be dependent on the lactose properties. Flowability of StarLac is dependent on the spray-drying process. Moreover, starch imparts its rapid disintegration property. Starlac was proven to have improved compactibility and flowability to starch and its physical mixtures. Gohel and Jogani demonstrated use of several linear regressions in development of co processed lactose and starch. The authors concluded that as the lactose: starch ratio increased, Carr's index of the adjuvant and crushing strength of the tablets increased although friability decreased. The percentage of starch paste has inverse effect on the friability. It is used in low-dosage and fast dissolving formulations, direct compression, Dry granulation, homeopathic formulation[9].

Pharmatose DCL 40: Anhydrous lactose is a free flowing and directly compressible crystalline material with no water of hydration. However, its fluidity is less than optimal as it contains high amount of fines. Furthermore, it picks up moisture to form the hydrated compound at relatively high humidity. This is often accompanied by an increase in the size of the tablets if the excipient makes up a large portion of total tablet weight. Coprocessing of anhydrous lactose (95%) with lactitol (5%) into Pharmatose DCL 40 has helped to overcome these problems. Its flow properties improve because of its spherical form and favorable particle size distribution. The water uptake of Pharmatose DCL 40 at increasing humidity is very low. Moreover, its binding properties and dilution potential are much better than those of all known lactose based products. [(9)]

Co processing of cellulose: MCC is a commonly employed direct compression excipients with good lubricity and low hygroscopicity. It has the highest dilution potential. When compressed, the MCC particles are deformed plastically due to presence of slip planes and dislocations on a microscale, and the deformation of the spray-dried agglomerates on a macro scale. However, MCC loses its compressibility on addition of water during wet granulation. This phenomenon is known as quasihornification. The loss of compressibility of MCC is particularly problematic when it is used in a major proportion in tablet. The fluidity of MCC is poor compared to that

of most of other direct-compression fillers because of its relatively small particle size.

Co processing of MCC (98%) with fumed colloidal silicon dioxide (2%) into SMCC **(Prosolv)** results in improved strength of tablet compacts and reduced sensitivity to wet granulation. SMCC has also better flowability than MCC. Fraser et al. Reported that there is no discernible chemical or polymorphic difference among the SMCC, MCC and dry mixes of MCC and silicon dioxide, indicating that the material produced by 'silicification' process is chemically and physically very similar to standard MCC. In spite of being very similar structures, analytical techniques such as near IR cannot provide an explanation for the improvements in compressibility of SMCC over MCC. Internal bonding in SMCC accounts for change in compressibility from MCC after wet granulation.

Luukkonen et al. studied the rheological behavior of the wet powder masses of SMCC (Prosolv), and standard grades of MCC (Emcocel 50 and Avicel PH 101) as a function of mixing time using a mixer torque rheometer. They found that SMCC has improved flow characteristics and specific surface area, whereas it reduced swelling compared to standard MCC grades. Bolhuis et al. reported a small negative effect of colloidal silicon dioxide on the interparticle bonding strength of unlubricated MCC. However, SMCC showed no significant effect on the tablet strength of lubricated tablets compared to physical mixtures. The strength of SMCC compacts was markedly increased with increasing compression force. Staniforth et al. Reported that compacts of SMCC exhibited greater strength and stiffness than those of MCC. Lahdenpaa et al have demonstrated that SMCC is useful when cohesive, poorly compressible ingredients are formulated into direct compressed tablets.

Kachrimanis et al found a slight increase in the tensile strength but a marked increase in the disintegration time of Prosolv compared with Avicel in the packing fraction range 0.7 – 0.9, the range for pharmaceutical tablets. The MCC grade or silicification affects the moisture sorption and the packing during tapping as well as the particle deformation during tabletting. The incorporated silicon dioxide acts as a barrier or sinks for the moisture sorbed only for relative humidity up to 52%. At higher relative humidity (72%), the incorporated silicon dioxide does not increase the particle deformation, and results in more extended disintegration time owing to its probable saturation.

Silicification also results in reduction of the adsorption of amine drug (tacrine hydrochloride) from aqueous solution onto MCC. Felton et al. found that SMCC containing capsules exhibited the lowest variation in weight, although these findings were not significantly different from either of the MCC-containing capsules. [10]

Avicel CE 15:

Avicel CE 15 is a coprocessed excipient of 85% MCC and 15%guar gum, mainly used in chewable tablets.Avicel CE 15 offers improved palatability, creamier mouthfeel with less grittiness and reduced tooth packing .[4,6,10,15]

Vitacel® : Coprocessing of 75% MCC with 25% calcium carbonate was carried out in a weight ratio from about 75:25 to 35:65. The product exhibits low lubricant sensitivity; its compression profile (tablet hardness versus tablet compression force) remains relatively unchanged when various lubricants are employed. This lubricant insensitivity extends both to lubricant level (amount) and lubricant type (magnesium stearate, stearic acid, etc.). Limwong *et al.* fabricated composite particles of rice starch and MCC by spray-drying technique and evaluated its direct compressibility. These composite particles exhibited good compressibility and flowability whereas its tablets show low friability and good self-disintegrating property. Thus, these developed composite particles could be introduced as a new co processed excipient compression excipient. [4, 8, 10]

Avicel HFE 102: Coprocessed product of MCC and mannitol has an improved compactibility profile, lubricant sensitivity and ejection profile compared to MCC. Shirwaikar *et al.* used spray drying technique for coprocessing of MCC and mannitol to obtain direct compression excipient. Mannitol and MCC in the ratio 1.25:1 was found to have optimized powder and compressibility characteristics with fast disintegrating property. Evaluatory study on disintegration time and mouthfeel attributes such as grittiness and chalkiness ranked the formulation as the best. [4,10]

Coprocessing of sugars and polyols : Sorbitol is widely used as the sole ingredient in sugar-free mints and as a vehicle in chewable tablets. It has a cool taste and good mouthfeel and forms relatively good compacts. But its highly hygroscopic nature leads to its poor powder flowabiltiy and caking, sticking during tabletting. Moreover, its hygroscopicity has its impact on the physical characteristics of tablets such as hardness, dissolution and bioavailability. On the other hand,

mannitol does not make as hard a tablet as sorbitol but is less sensitive to humidity. Compressol S, a directly compressible excipient of sorbitol and mannitol retains the compactibility of sorbitol and characteristic mannitol texture with lower hygroscopicity than sorbitol. Compressol S is 300 times less hygroscopic than sorbitol, which makes it more suitable to use with moisture-sensitive drugs. This product is designed to assist the formulator with high active loading formulations and difficult to compress actives. Good compactibility and low hygroscopicity combined with pleasant taste and favorable mouthfeel of Compressol S makes it ideal for use in chewable and high dose active nutraceutical tablet formulations . The coprocessed excipient of mannitol and sorbitol can also successfully be included in quick dissolving tablet formulations.[10]

Advantose FS 95: Fructose is a monosaccharide widely available from nature having very desirable sweetness and a natural food orientation that makes it suitable to use in pharmaceutical formulations. Fructose is, however, not directly compressible. Fructose granules agglomerated from a water solution are hard and the compressibility is unsatisfactory. Advantose FS 95 direct compression fructose is a co-dried system of fructose and a small amount of starch, which turns fructose into an excellent excipient for pharmaceutical, nutraceuticals and chewable vitamin applications. The particle size distribution of Advantose FS 95 fructose significantly improves the flow properties. The Advantose FS 95 product has lower hygroscopicity than standard fructose, making it easier to handle with improved compressibility. ([10])

Dipac : Di-Pac is a directly compressible, co-crystallized sugar consisting of 97% sucrose and 3% modified dextrin. It is a free flowing, agglomerated product consisting of hundreds of small sucrose crystals glued together by the highly modified dextrin. At high moisture level, Di-pac begins to cake and loose its fluidity. Tablets containing a high proportion of Di-pac tend to harden after compression at higher relative humidity. Its sweet taste makes it suitable for most directly compressible chewable tablets. Rizzuto et al., demonstrated that co-crystallized sucrose and dextrin deformed readily by plastic fracture to provide much harder compacts than those obtained from sucrose crystals alone .Used as sweetener (10-50%), dry binder (5-20%), filler (20-60%) etc. Used in direct compression, Chewable tablets. [4,5,12]

Xylitab ®: coprocessed directly compressible excipient of xylitol and sodium caboxymethyl cellulose is marketed as Xylitab ® (Danisco A/S, Copenhagen, Denmark). Xylitab has a cool taste, great stability and is ideal for all tablet forms. Morris et *al.* Evaluated Xylitab 100 and Xylitab 200 for compaction, flow, lubrication requirements and dilution potential. Compaction profiles, flow behavior, and dilution potential of xylitab was found to be acceptable and the authors concluded that xylitab can be successfully utilized as direct compression chewable tablet excipient. [8, 10]

Coprocessing of inorganic fillers[30,33,57]: Coprocessing of calcium carbonate (70%) with sorbitol (30%) (Formaxx) offers a distinct advantage of producing directly compressible calcium carbonate. Formaxx offers improved flowability, superior compaction properties at low compression forces and has low friability compared to calcium carbonate. This unique processing of calcium carbonate with sorbitol masks the chalky and gritty taste of calcium carbonate. Freitag *et al.* showed that coprocessing of magnesium carbonate with 5% powdered cellulose seems to be a promising excipient for direct compression. This coprocessed product combines good flow and tablet properties, and is superior to pure magnesium carbonate or their physical mixture .[10]

Ludiflash: 90% Mannitol, 5% (Crospovidone) 5% (polyvinyl Acetate).It is specially designed for directly compressible, high speed tableting and hard tablet with very low friability. It has good flowability, less water absorption.[4,8]

Orocell 200 & Orocell 400: Composition - Spheronised mannitol with different particle size. Orocell 200 with 90% mannitol (<315µm) Orocell 400 with 90% mannitol (<500µm).

Characteristics - A developed filler-binder with high dilution potential and good disintegrating property useful for orally disintegrating tablets. [4]

StarLac[39]: A co processed spray dried filler/binder for direct compression and composed of a-lactose monohydrate and Maize-starch. The new product should combine the good flowability and plastic deformation of spray-dried lactose with the elastic deformation and rapid disintegration of native maize starch. StarLac demonstrated good compactibility and release behaviour. It exhibited deformation behaviour with higher parts of plastic and elastic deformation than FlowLac, therefore StarLac is of interest for the manufacture of pressure sensitive drugs. The advantage of Starlac are its

good flowability depending on the spray-drying process, an acceptable crushing force due to its lactose content, its rapid disintegration depending on starch. Gohel and Jogani demonstrated use of multiple linear regression in development of co-processed lactose and starch. Authors concluded that as the lactose/starch ratio increased Carr's index of the adjuvant and crushing strength of the tablets increased while friability decreased. Percentage of starch paste has inverse effect on the friability.[4,5,8]

Table No 1 Flow properties of various co processed excipients.

Trade name	Particle size distribution	Hausner ratio	Bulk Density (g/cm ^{3})	Tapped density (g/cm^3)	Angle of repose	Compressibility index
Ludipress	< 63 µm max. 20% < 20 µm 40 – 65% 400 µm max. 20%	1.20	0.517	0.618	29.5^o	16.14
Cellactose	<32 µm <=20% <160 µm 35-65% <200 µm >=80%	1.24	0.38	0.5	32-35^o	17.75
MicroceLac100	<32 µm <=15% <160 µm 70% <250 µm >=90%	1.16	0.5	0.6	34^o	
Starlac	< 32 µm NMT 15% < 160 µm 35 – 65% < 250 µm NLT 80%	1.19	0.57	0.68	<=29^o	16.18
Pharmatose DCL 40	< 45 µm max. 20%< 150 µm 40 – 65%	1.27	0.67	0.85	<=39^o	21.18

CONCLUSION:

Co-processed excipients are the trend to introduce new functionalities and minimize variability with minimum data burden to improve the performance of tableting process.They can be custom designed to possess specific characteristics and functionality for specific applications. The future for co-processed excipients looks very promising. With upcoming newer combination of excipients and newer methods of coprocessing, co-processed excipients are for sure going to gain attraction in developing different dosageforms in pharmaceutical industry.

REFERENCES:

1. Ajay Subhash Chougule, Amrita Dikpati and Tushar Trimbake Formulation Development Techniques of Co-processed Excipients Journal Of Advanced Pharmaceutical Sciences Vol.2/Issue.2/2012
2. Chowdary K P R, Ramya K. Recent Research on co-processed excipients for direct compression – A-Review. Intr. J. Clinical Pharam. 2013; 2(1):1-5.
3. Satish K. Nachaegari and Arvind K. Bansal coprocessed excipients for solid dosage forms Pharmaceutical Technology JANUARY 2004; 52-54.
4. M.Sujatha Kumari, CH. Prasanthi, CH. Sudha Bhargavi, M.Praveena Kumari, S.Ushasri. Reassessment Of Novel Co-processed Multifunctional Excipients International Research Journal Of Pharmaceutical And Applied Sciences (IRJPAS); 2013; 3(4):122-128
5. Patil Atul, Kundu Subrata, Srinivasan Ganga ; A Review On Co-processed Excipients: A Novel Approach In Formulation Development :Volume 3, Issue 5, September _ October 2013
6. Sreekanth Babu S, Ajay Kumar A, Suman D R :Co-processed Excipients: A Review International Journal Of Current Trends In Pharmaceutical Research Ijctpr, 2013: Vol. 1(3): 205-214
7. Belda PM and Mielck JB. The Tableting Behavior of Cellactose Compared with Mixtures of Celluloses with Lactoses. Eur J Pharm Biopharm, 1996; 42 (5): 325–330.
8. Hauschild K and Picker KM. Evaluation of a New Coprocessed Compound Based on Lactose and MaizeStarch for Tablet Formulation. AAPS Pharm Sci, 2004; 6 (2): 1-12.
9. Sumit Saha & Aliasgar F Shahiwala Multifunctional coprocessed excipients for improved tabletting performance: Expert Opin. Drug Deliv. (2009) 6 (2):197-208
10. Guo J,Lactose in pharmaceutical applications, Drug Del.Technol,4
11. Whiteman,M,and Yarwood,R J, Evaluation of six lactose-based materials as direct compression tablet excipients,Drug Dev Ind Pharm,14:1023-1040,1988
12. Gohel MC and Jogani PD. An Investigation in Direct Compression Characteristics of Co-processed Lactose and Starch using Experimental Design, Indian J. Pharm. Sci. 2003 65: 31-38.

13. Shangraw RF, Direct compression Tableting Encyclopedia of Technology, Vol-4,Marcel Dekker ,USA,2nd ed,85-160,1988.
14. K P R Chowdary and K Ramya Recent Research On Co-processed Excipients For direct Compression-a Review International Journal Of Comprehensive Pharmacy Vol. 04, Issue 02
15. Armand Michoel, Patrick Rombaut, Comparative Evaluation of Co-processed Lactose and Microcrystalline Cellulose with Their Physical Mixtures in the Formulation of Folic Acid Tablets, 2002, Vol. 7, No. 1, Pages 79-87
16. Karsten Hauschild, Evaluation of a new coprocessed compound based on lactose and maize starch for tablet formulation. AAPS PharmSci 02/2004
17. Minakshi Marwaha, Deepak Sandhu, Rakesh Kumar Marwaha, "Co processing of excipient: A review on excipient development for improved tabletting performance" International Journal of Applied Pharmaceutics, 2(3), 2010, 41-47
18. The future of coprocessed excipients : Dave Schoneker/Brain Carlin 6th may 2010
19. Ipec Europe: Co-Processed Excipients: Regulatory Challenges. Carl Mroz ,Coloron Limited ,June 2009.
20. Neha Kanojia, Loveleen Kaur, Manju Nagpal and Rajni Bala Modified Excipients In Novel Drug Delivery System: Need Of The Day Journal Of Pharmaceutical Technology, Research And Management. Vol : 1,May 2013 Pp: 08.
21. Jacob S, Shirwaikar A A, Joseph A, Srinivasan K K; Novel co-processed excipients of mannitol and microcrystalline cellulose for preparing fast dissolving tablets of glipizide. Indian J Pharm Sci. 2007; 69:633639.
22. Mourya K, Prajapati S K, Jain S K, Kumar A, Thakran A K and Alok S; Formulation and Evaluation of Fast Dissolving Tablets of Acetaminophen. IJPSR. 2012; 3(2):610-614.
23. Marta Casalderrey, Consuelo Souto, Angel Concheiro, Jose Gomez-Amoza, and Ramón Martínez-Pacheco; A Comparison of Cellactose with Two ad hoc Processed Lactose-Cellulose Blends as Direct Compression Excipients. Chem Pharm Bull. 2000; 48(4):458-463.
24. Minakshi Marwaha, Deepak Sandhu, Rakesh Kumar Marwaha; Coprocessing of Excipients:A Review on Excipient Development for Improved Tabletting Performance. International Journal of Applied Pharmaceutics. 2010; 2(3):41-47.
25. Gonnissen Y, Remon JP, Vernaet C. "Developement of directly compressible powders via co-spray drying." Eur.J.Pharm. Biopharm., 2007, 67, 220-226.
26. Gonnissen Y, Gonc alves S.I.V, Geest B.G. De, Remon JP, Vervaet C, "Process design applied to optimise a directly compressible powder produced via co-spray drying," Eur. J.Pharm. Biopharm. 68, 2008, 760–770.
27. Chougule Ajay Subhash, Dikpati Amrita and Trimbake Tushar. "Formulation Development Techniques of Co-processed Excipients." JAPS/Vol.2/Issue.2/2012 page no. 231-249
28. Gohel M, Jogani Pranav D, "A review of co-processed directly compressible excipients," J. Pharm Pharm. Sci. 8(1) 2005: 76-93.
29. M.Sujatha Kumari, Prasanthi , CH. Sudha Bhargavi, M.Praveena Kumari, Ushasri S. "Reassessment of Novel Co-Processed Multifunctional Excipients" Int. Res J Pharm. App Sci., ISSN: 2277-4149 2013; 7(4):122-128
30. Chowdary KPR, Ramya K, "Recent Research on co-processed excipients for direct compression-A REVIEW." Pharm Globale (IJPC) Vol.04, Issue 02 ISSN 0976-8157 2013. 1-5
31. Patel Rakesh P, Int.J. PharmTech Res, "Directly Compressible Materials via Co-Processing." ISSN : 0974-4304 Vol.1, No.3, 745-753 , July-Sept 2009
32. Patel SS, Patel NM, "Development of directly compressible co-processed excipient for dispersible tablets using 3^2 full factorial design." Int. J pharm pharm sci. 2009; 1(1):125-148
33. Aundhia C.J, Raval J A, Patel M.M, Shah N.V, Chauhan S.P, Sailor G.U, Javia1 A.R, Mahashwari R.A, "spray drying in the pharmaceutical industry-A review" Indo American J. Pharma Res. 2011:7(1);125-138
34. Afoakwah A N, Adomako C, Owusu J. Engman N. F, Hannah A. "A Spray Drying as an Appropriate Technology for the Food and Pharmaceutical Industries - A Review." JECET; September-November, 2012; Vol.1.No.3, 467-476.
35. Marwaha Minakshi, Sandhu Deepak, Marwaha Rakesh Kumar. "Coprocessing of excipients: a review on excipient development for improved tabletting performance." Int J. App Pharm, Vol 2, Issue 3.2010 41-42
36. Awasthi Rajendra, Sandhu Deepak, Garg Garima, Pawar Vivek, Sharma Gaurav, Kulkarni Giriraj T, "Development of directly compressible co-processed excipients for solid dosage forms." Scholar Research Library. ISSN 0975-5071 USA CODEN: DPLEB4, Der Pharmacia Lettre, 2010, 2(6): 151-165
37. www.wikipedia.org/wiki/Co-processing
38. Gohel MC, and Jogani PD. An Investigation in Direct Compression Characteristics of Co-processed Lactose and Starch using Experimental Design, Indian J. Pharm. Sci. 2003 65: 31-38.
39. AK Olowosulu, O Avosuahi, AB Isah, MA Ibrahim. Formulation and Evaluation of Novel Coprocessed Excipients of Maize Starch and Acacia Gum (StarAc) For Direct Compression Tabletting, International J. of Pharmaceutical Research and Innovation, Vol. 2: 2011 39-45, 39.
40. T Baykara, G Duman, KS Ozesener, S Ordu, and B Ozates . Comparing the Compressibility of Ludipress with the other Direct Tabletting Agents by Using Acetaminophen as an Active Ingredient, Drug. Dev. Ind. Pharm., 17: 2359-2371.1991
41. Ramani Rashmin G, "Development of Novel Coprocessed Excipients for the Design and Evaluation of Fast Dissolving Metoclopramide Hydrochloride Tablets" Department of pharmaceutical technology, H.K.E. Society's college of pharmacy.2010, 5-105
42. Jacob S, Shirwaikar A A, Joseph A, Srinivasan K K; "Novel co-processed excipients of mannitol and microcrystalline cellulose for preparing fast

dissolving tablets of glipizide." Indian J Pharm Sci. 2007; 69:633-639.
43. Jacob S, Shirwaikar A A, Joseph A, Srinivasan K K, "Novel co-processed excipients of mannitol and microcrystalline cellulose for preparing fast dissolving tablets of glipizide." Indian J Pharm Sci. 2007; 69:633-639.
44. Gohel M C, Parikh Rajesh K, Prajapati Manali D, Zala Bhavika H, "Preparation and Evaluation of Material Properties of Co-processed Diluent Containing Modified Starch and Dicalcium Phosphate." IJPSR. 2011, 2(3):543-551.
45. Patel SS, Patel NM, Soniwala MM, "Statistical Development of a Multifunctional Directly Compressible Co-processed Excipient Using the Melt Agglomeration Technique." Asian J.pharm sci. 2009 4(6):340-356.
46. Avachat Amelia, Ahire V J, "Characterisation and Evaluation of Spray Dried Co-processed Excipients and Their Application in Solid Dosage Form." Indian J Pharm Sci. 2007; 69:85-90.
47. Ayyappan J, Umapathi P, Darlin quine, "Development and Evaluation of a Directly Compressible Co-processed Multifunction Sustained Release Agent for Tablets." Int J Pharma Sci. 2010; 2(4):201-205.
48. Nidal Daraghmeh, Iyad Rashid, Mahmoud M H Al Omari, Stephen A Leharne, Chowdhry Babur Z, Adnan Badwan; "Preparation and Characterization of a Novel Co-processed Excipient of Chitin and Crystalline Mannitol" AAPS pharm sci tech. 2010; 11(4):1558-1571.
49. Gohel Mukesh C, Review on Spray Drying; Available on www.pharminfo.net
50. Robert E O'Connor, Linda A Felton, Joseph B Schwartz. Powders. In, David Troy (ed). Remington The Science and Practice of Pharmacy,21st Edition. Baltimore, Philadelphia. Lippincott Williams & Wilkins., 2005; 702.
51. Spray Drying scale up from research to industrial production. Available on http://www.niroinc.com/html/pharma/phpdfs/spray_drying_scale_up.pdf.
52. KP Hapgood, MXL Tan, DWY Chow . A method to predict nuclei size distributions for use in models of wet granulation, Advanced Powder Technology.2009 20: 293–297.
53. FP York, RC Rowe. Process control and scale-up of pharmaceutical wet granulation processes: a review, European Journal of Pharmaceutics and Biopharmaceutics. 52. 2002 : 269–277
54. www.wikipedia.org/wiki/spray_drying
55. Mukesh C. Gohel ; Review on Spray Drying; Available on www.pharminfo.net
56. M.Maury,K. Murphy,S. Kumar,L. Shi andG. Lee, Effects of process variables on the powder yield of spray-dried trehalose on a laboratory spray dryer. Eur. J. Pharmac. & Biopharm, 2005. 59, 565–573
57. FORMAXX® Pdf is available online the given link 85.238.144.18/lifescience/literature/Formaxx%20Coprocessed%20Calcium%20Carbonate.pdf