The Unique DCPA

Fujicalin®

Dibasic Calcium Phosphate Anhydrous designed to function as a direct compression excipient with high exceptional flow and compression characteristics

Fuji Chemical Industries

Table of Contents

Introduction

Fujicalin® is a dibasic calcium phosphate anhydrous designed to function as a direct compression excipient. It has exceptional flow and compression characteristics, while maintaining the ability for rapid disintegration. The key to Fujicalin®'s superior performance is the highly specialized and proprietary manufacturing process that yields a unique primary particle.

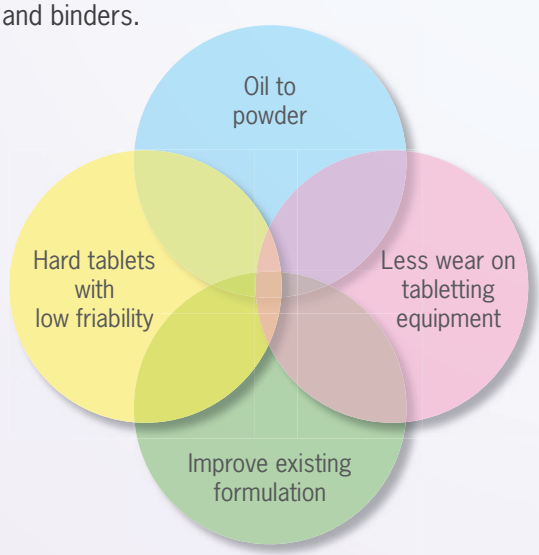
The patented manufacturing process yields porous spheres with high specific surface area. Fujicalin® is totally synthetic and ideally suited to direct compression formulations, especially involving difficult-to-compress materials like oily actives.

It can also be used to assist flow, reduce tablet weight variation and improve content uniformity.

Fujicalin®'s compressibility facilitates the design of smaller tablets. It can also be used as a partial or total replacement for microcrystalline cellulose.

Characteristics

1. Fujicalin® is a synthetic, free flowing spherically granulated Dibasic Calcium Phosphate Anhydrous (DCPA) for direct compression of tablets.
2. Fujicalin®'s patented manufacturing process yields porous spheres with a high specific surface area, 20 to 70% more than conventional Dibasic Calcium Phosphate excipients.
3. Fujicalin® has a low mean particle size of 120 µm. The granules are highly stable and compact to tablets of higher tensile strength.
4. Fujicalin®'s smooth and spherical granules are less abrasive on tabletting machines leading to trouble free operations.
5. Fujicalin®'s porosity and extremely high specific surface area allows formulators to develop oral dosage forms of oily actives. It is an ideal excipient for liquid solid system.
6. Fujicalin®'s anhydrous nature results in very low water of crystallization thus making it the ideal choice for hydrolysable drugs.
7. Fujicalin® makes sufficiently hard tablets at low compression forces and in addition, improves the hardness of other fillers and binders. It is an ideal excipient for manufacturing tablets of probiotic preparations.
8. Fujicalin® retains porosity at high compression forces and exhibits low friability across broad compression range.
9. Fujicalin® is ideal as a carrier for Self Emulsifying Drug Delivery System (SEDDS) and solid dispersion including Hot Melt Extrusion (HME).
10. Fujicalin® is suitable for both pharmaceutical and food applications.



The core benefits of incorporating Fujicalin® as an excipient

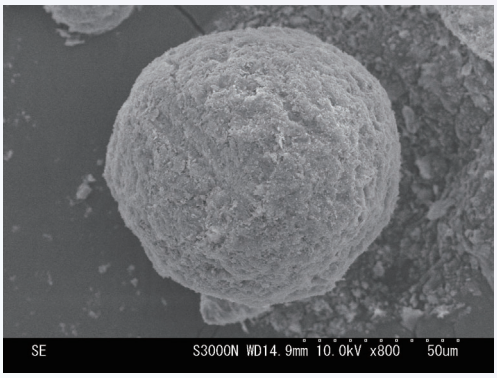
Chemical Formula

$CaHPO_4$

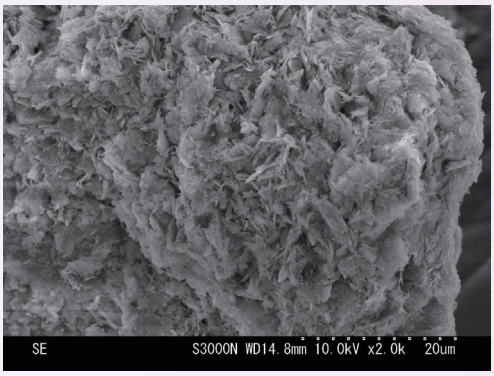
Spray Dried Granules

Dibasic Calcium Phosphate Anhydrous; Calcium Hydrogen Phosphate, Anhydrous

Electron micrographs of Fujicalin®



Fujicalin® (x800)



Fujicalin® (x2,000)

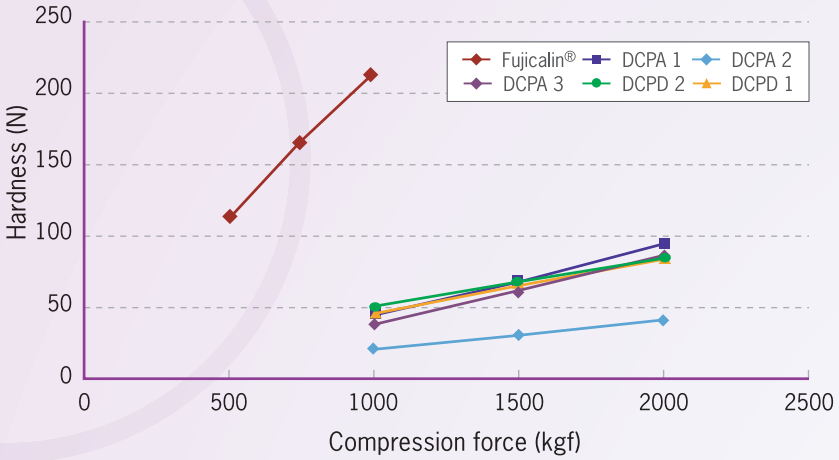
General Properties

General Properties of Fujicalin®

Properties		**Fujicalin®**
Appearance		White Crystalline Powder
Mean particle size (µm)		120
Bulk density (g/ml)	Loose	0.46
	Tapped	0.54
Compressibility index		15.1
Angle of repose (°)		29.5
Angle of spatula (°)		33.3
Carr value*		86.5
BET surface area (m^2/g)		40
Oil adsorption capacity (ml/ g)		1.1
Water adsorption capacity (ml/ g)		1.2
Loss on drying		0.5
Flowability		Excellent
Water activity		0.11

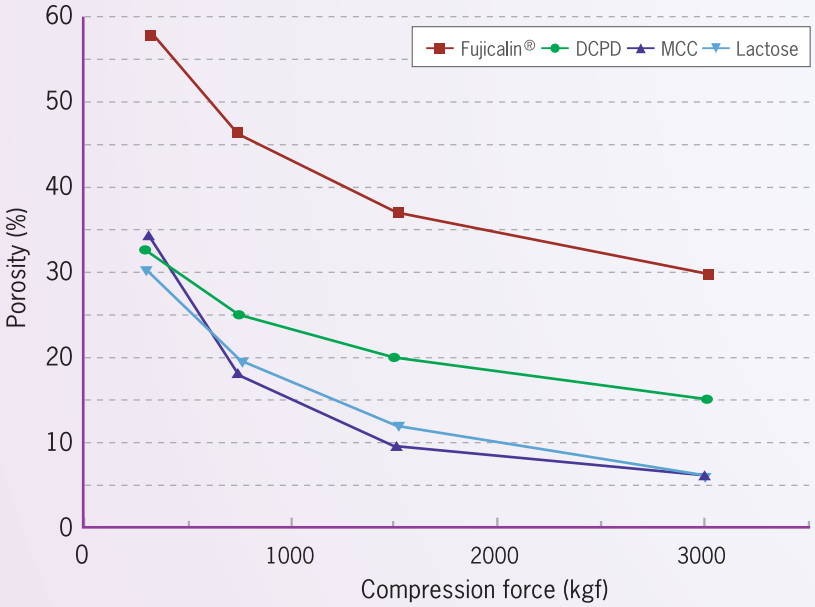
*Carr value calculated adding relevant index points. Higher value indicates better powder flow properties (Ref- Carr, R. L., Chem. Eng., 1965; 72(3), 163-168)

Comparison of tablet hardness with other available DCPA's



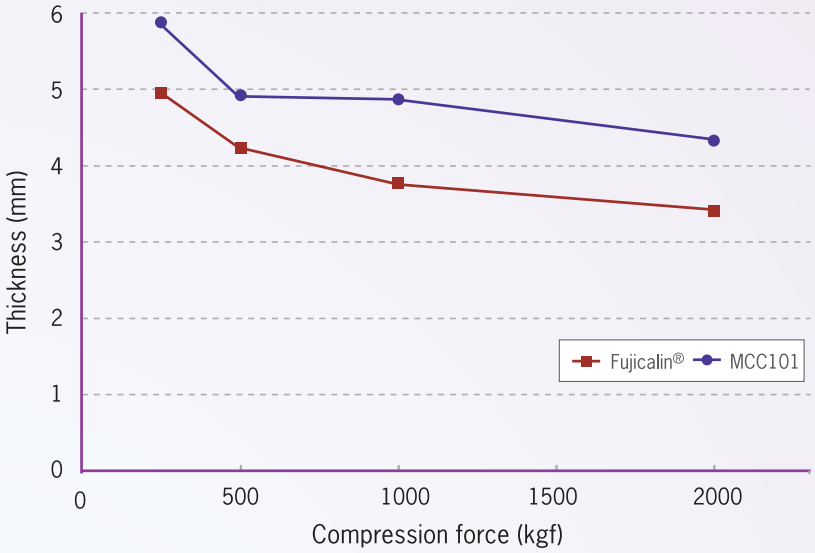
Fujicalin®'s high specific surface area contributes to higher tablet hardness at low compression forces.

Porosity retention of placebo tablets

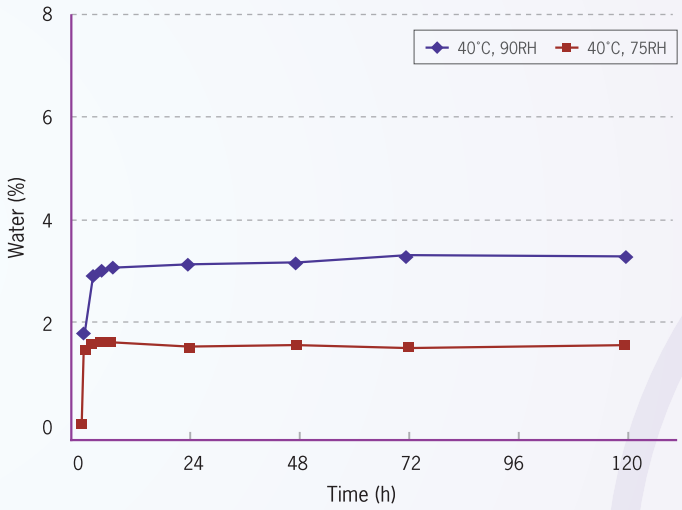


Fujicalin® retains high porosity at relatively high compression forces. High porosity contributes to faster disintegration and dissolution of tablets.

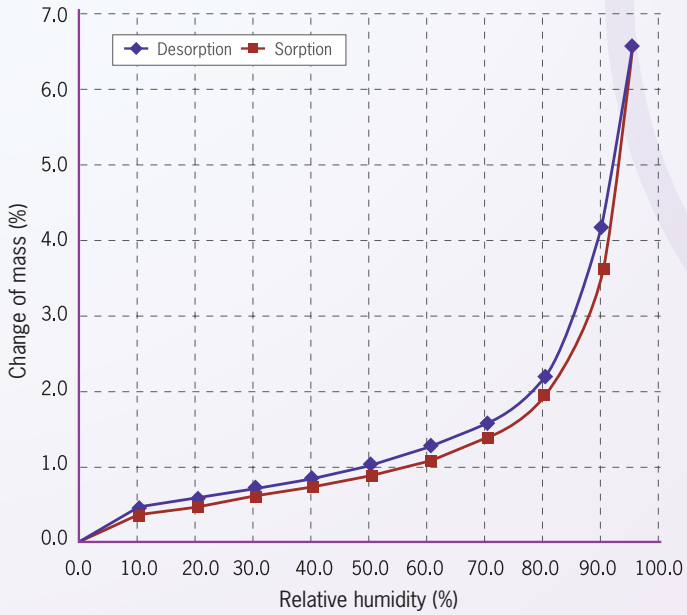
Fujicalin® can produce compact and thin tablets



Hygroscopic equilibrium curve of Fujicalin®



Moisture sorption-desorption curve of Fujicalin®



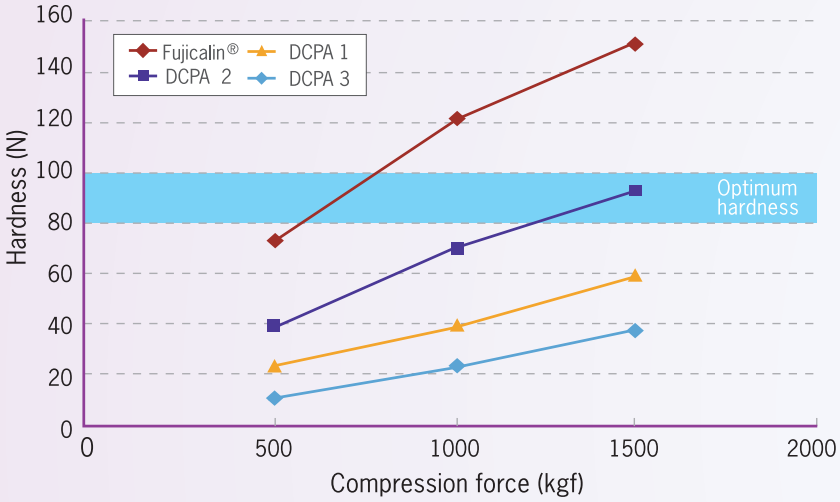
Application

I. Converting Oil and extracts to free flowing Powder

A. Tablets of Boiled linseed Oil

Converting oily actives into a free flowing powder which can be processed into capsules or tablets is a great challenge to formulators. The oil load may affect flowability, compactability and compressibility leading to poor quality tablets. Boiled linseed oil, a recommended oil for testing oil adsorption properties was adsorbed on to Fujicalin® and other available DCPA's. Fujicalin® showed excellent compressibility by achieving an optimum tablet hardness of 80 to 100 N at very low compression forces.

Tablet hardness of Fujicalin® and other commercially available DCPAs at different compression forces (ø11.3mm, 600 mg per tablet)



B. Tablets of Vitamin E

Vitamin E is a fat soluble vitamin like A, D and K. It is oily in physical appearance and exists either in the form of tocopherols or tocotrienols. 12.5 g of Vitamin E was diluted with same amount of ethanol and mixed well before loading on to 83.5 g of Fujicalin® or other grades of DCPAs. The mixture was dried overnight in an oven at 50°C. Fujicalin® produced high quality Vitamin E tablets with sufficient tablet hardness (80-100 N) at low compression forces of 200-500 kgf. To achieve an optimum hardness of 80-100 N, other DCPA's need to be compressed at higher forces.

Powder characteristics after 12.5% Vitamin E load

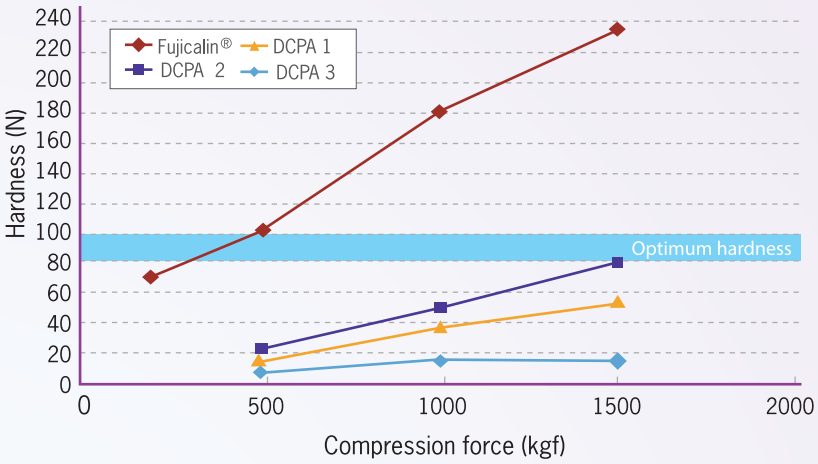
Comparison data with other DCPAs

	Fujicalin®		DCPA 1		DCPA 3	
	Before	After	Before	After	Before	After
Angle of repose (°)	29.5	28.1	30.5	39.0	37.1	39.9
Compressibility index	15.1	11.6	11.8	18.3	14.9	19.7
Angle of spatula (°)	33.3	24.8	47.5	49.2	37.8	54.0
Degree of uniformity	1.8	6.5	1.6	16.9	2.2	11.2
Carr value*	86.5	92.0	82.0	67.0	80.5	69.0
Flowability	Excellent	Excellent	Good	Poor	Good	Poor

*Carr value calculated adding relevant index points. Higher value indicates better powder flow properties
(Ref- Carr, R. L., Chem. Eng., 1965; 72(3), 163-168)

Tablet hardness after Vitamin E adsorption

Comparison data with other DCPAs



Fujicalin®'s powder properties in fact showed improved values after Vitamin E adsorption. Superior Carr value validates the efficiency of Fujicalin® in converting oily actives like vitamin E into a free flowing powder when compared to other DCPA's.

II. Blending and content uniformity of active ingredients

A. Blending of two different particle sizes of acetaminophen

Two different particle sizes of acetaminophen were blended using two different blending machines to study the content uniformity.

Fujicalin® Blending Characteristics

	D50 (µm)	Twinshell blender		High shear mixer	
		SG150	SG100	SG150	SG100
Acetaminophen	148.6	20	-	20	-
	98.6	-	20	-	20
Fujicalin®	115.1	64	64	64	64
L-HPC*	40.4	15	15	15	15
Magnesium Stearate	-	1	1	1	1
Total (%)		100	100	100	100

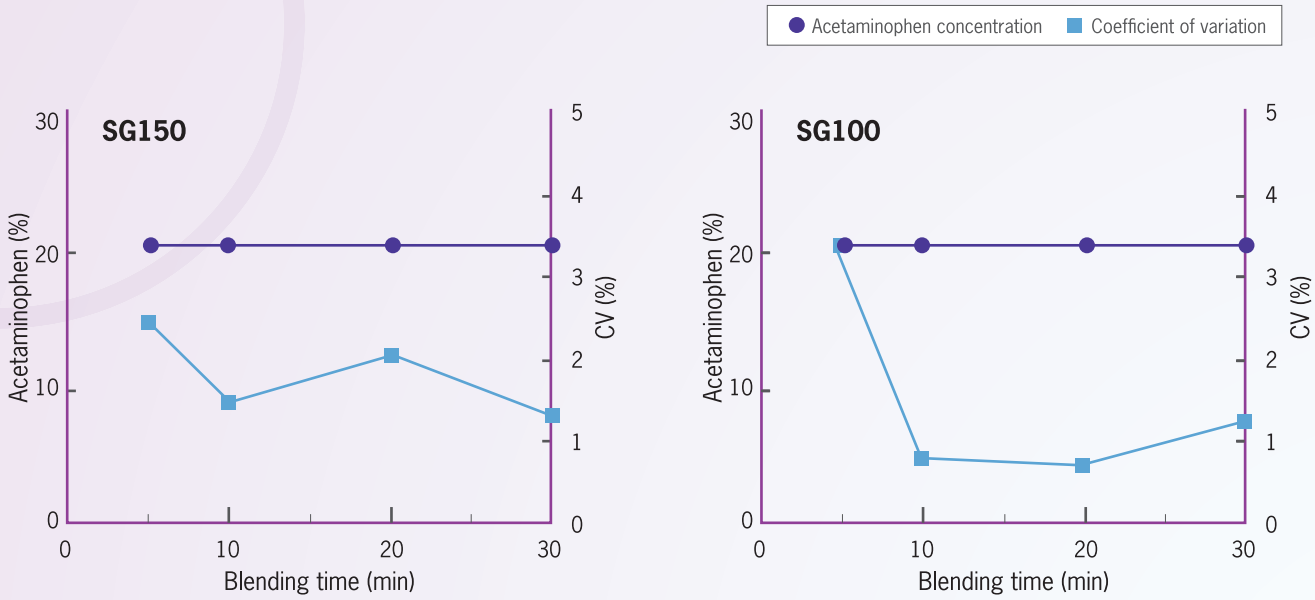
*L-Hydroxypropyl cellulose

Method

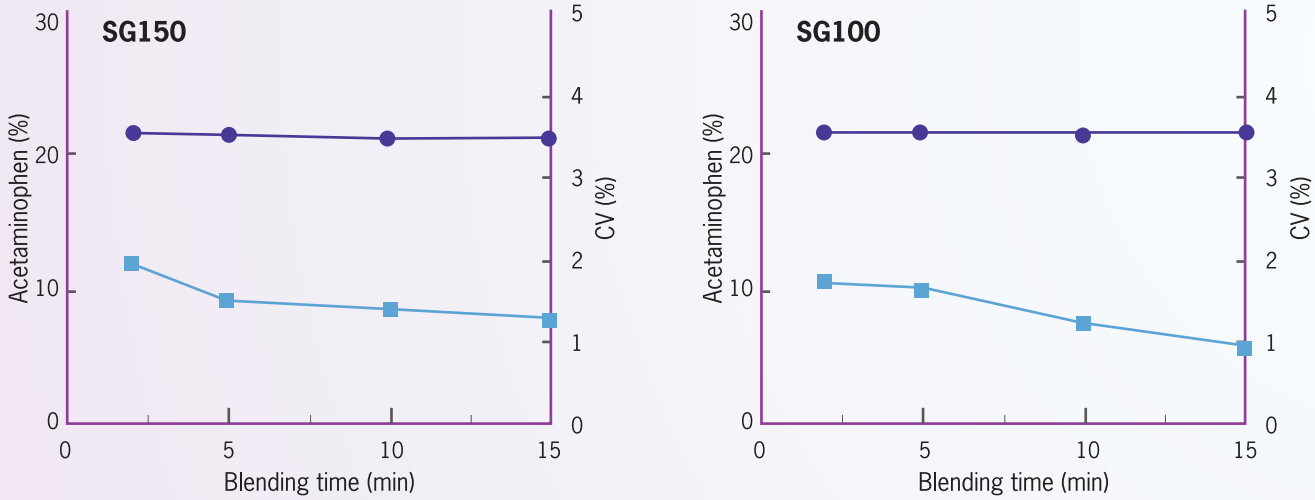
- Mix the materials in the above formulation by twinshell blender (V-type mixer) or high shear mixer.
- Sample at the set intervals.
- Compress the mixed powder with rotary tabletting machine.
- Sample at 0, 2.5 and 5 hours.

Faster blending of different particle sizes of acetaminophen

Twinshell Blender



High Shear Mixer

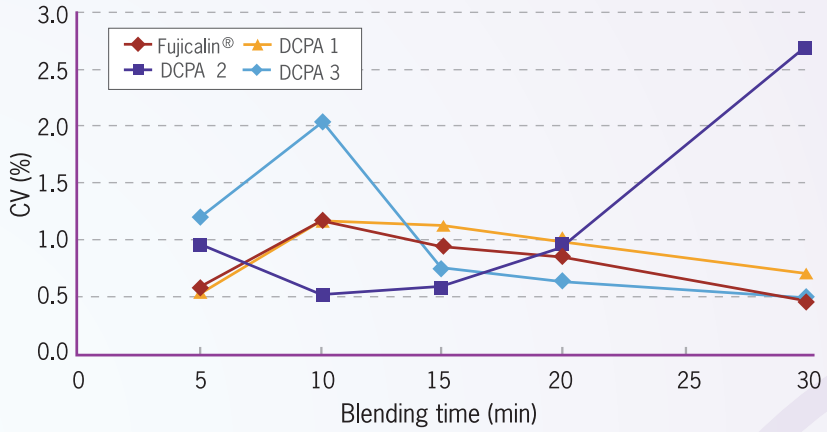


Blending 20% acetaminophen with Fujicalin® in a twinshell blender and high shear mixer showed very good content uniformity as indicated by CV % and acetaminophen content of the tablets.

B. Blending of micronized low density acetaminophen

Micronized drug substances may exhibit increased cohesiveness and have a tendency to segregate in blending. Acetaminophen tablets were prepared by direct compression with Fujicalin® and three other DCPA's. Blending of micronized acetaminophen powder (14 µm) and DCPA's were carried out for 30 minutes in a 2 liter V shaped low shear blender.

Fujicalin® showed easy blending character when compared to other DCPA's



Fujicalin® maintained a low CV with increased blending time.

Application In Probiotics

Probiotic products available in the market are mostly in liquid or semisolid formulations which show low cell viability during storage and after oral administration, mainly because the bacteria do not survive low pH conditions. Probiotic formulations require low water content and low temperature during storage in order to preserve cell viability.

Development of oral solid dosage forms by direct compression which enable higher bacterial survival is a strategy to solve the problem. Oral solid dosage forms by direct compression have many advantages such as greater stability, accurate dosage, easy production but not all of directly compressible excipients are suitable for probiotic or lactic acid bacteria formulations.

Fujicalin® is highly recommended for developing tablets of probiotics which can be stored at room temperature. The shelf life of these preparations can be as long as three years. With spherical shape and smooth surface, Fujicalin® is highly flowable and has excellent blending capacity which increases content uniformity of probiotic formulations. Working well at low compression forces, Fujicalin® allows production of hard tablets with high cell viability as less heat is produced during the tabletting process. With a card-house structure which is easily collapsed, Fujicalin® breaks down into micromeric particles on applying pressure and entraps bacteria within, thus protecting the bacterial cells against harsh conditions during tabletting as well as in the stomach. Probiotic tablets of *Bacillus subtilis, Streptococcus faecalis*, and *Bifidobacteria* with Fujicalin® are commercially available with normal bottle packaging and can be stably stored at room temperature for 3 years.

A Typical formulation example of probiotic formulation

Components	**Quantity(%)**
Bacillus subtilis	10
Streptococcus faecalis	
Bifidobacteria	
Vitamins	0.1
Digestive enzyme	1
Dibasic calcium phosphate anhydrous	50 - 60
Sugars	25-35
Lubricant	4

Package Size

Fujicalin® is available in 20 kg aluminum bag in a Kraft bag.

Samples are available upon request. Please contact your local distributor or sales person.

Stability

Fujicalin® is a stable inorganic compound and meets EP, USP/NF and JP specifications. It is stable for 3 years from the date of manufacture.

Pharmacopoeia and Regulatory Information

Fujicalin® is manufactured under strict quality control at our GMP certified facilities. Fujicalin® meets all the requirements of the current USP/NF, EP and JP. A US DMF type IV filed in 1998.

Conclusions

Fujicalin® is a dibasic calcium phosphate anhydrous designed to function as a direct compression excipient which shows exceptional flow and compression characteristics. Spray drying makes Fujicalin® highly spherical and smooth particles with considerably less abrasiveness. Fujicalin® allows formulators to develop high quality tablets of oily API's, heat and moisture sensitive APIs, pH sensitive API's, probiotics, solid dispersions and other problematic formulations.

Further reading

1. Prajapati ST. *et al.*, Formulation and Evaluation of Liquisolid Compacts for Olmesartan Medoxomil. J Drug Deliv. 2013: 2013:ID 870579.
2. Sohn Y. *et al.*, Development of self-microemulsifying bilayer tablets for pH-independent fast release of candesartan cilexetil. Pharmazie. 2012; 67:917-24.
3. Hentzschel CM. *et al.*, Comparison of traditional and novel tableting excipients: Physical and compaction properties. Pharm Dev Technol. 2012; 17:649-53.
4. Hentzschel CM. *et al.*, Suitability of various excipients as carrier and coating materials for liquisolid compacts. Drug Dev Ind Pharm. 2011; 37:1200-7.
5. Kang MJ. *et al.*, Immediate release of ibuprofen from Fujicalin®-based fast-dissolving self-emulsifying tablets.a Drug Development and Industrial Pharmacy. 2011; 37:1298-305.
6. Hiroshi S. *et al.*, Formulation of lactic acid bacterium dosage form -Challenging for the unmanned direct compression. Pharm Tech Japan. 2009; 24: 27-32.
7. Hasegawa M. Evaluation of dibasic calcium phosphate for direct compression. Proc. Standard Formulation Res Assoc. 2007; pp 31-34.
8. Schüssele A and Bauer-Brandl A. Note on the measurement of flowability according to the European Pharmacopoeia. Int J Pharm. 2003; 257(1-2):301-4.
9. Schlack H. *et al.*, Properties of Fujicalin®, a new modified anhydrous dibasic calcium phosphate for direct compression: comparison with dicalcium phosphate dihydrate. Drug Dev Ind Pharm. 2001; 27(8):789-801.
10. Branchu S. *et al.*, A novel Dibasic Calcium Phosphate Anhydrous as an excipient for powderized DLα Tocopherol acetate. Pharma Sci. 1999; 1(4): no.2345.
11. Takami K. *et al.*, Novel preparation of free flowing spherically granulated dibasic calcium phosphate anhydrous for direct tabletting. Chem Pharm Bull. 1996; 44 (4): 868-870.

Fujicalin®

09.2015