International Journal of Pharmacy and Biological Sciences
ISSN: 2321-3272 (Print), ISSN: 2230-7605 (Online)
IJPBS | Volume 7 | Issue 2 | APR-JUN| 2017 | 79-92
Research Article – Biological Sciences| Open Access| UGC Approved | MCI Approved Journal

DEVELOPMENT AND EVALUATION OF CHLORPHENIRAMINE MALEATE ORALLY DISINTEGRATING TABLETS AND ORO DISSOLVING FILMS

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ABSTRACT

To prepare orally disintegrating tablet formulation of Chlorpheniramine maleate by wet granulation, direct compression in order to achieve rapid disintegration time and mask the bitter taste of the drug. To prepare oro dissolving films of Chlorpheniramine maleate by solvent casting method using two different polymers to achieve rapid disintegration time by using techniques like Freeze-Drying or Lyophilization, Tablet Molding, Cotton Candy Process, Mass-Extrusio. The rapid drug dissolution observed for direct compression than wet granulation, it may be due to easy breakdown of particles and rapid absorption of drug into the dissolution medium. Based on the above results the tablets prepared with wet granulation take more time to release the drug than direct compression. Based on the disintegration results direct compression techniques were more efficient than wet granulation technique. So that wet granulation technique not suitable for preparation of orally disintegrating tablets.

KEY WORDS

Oral disintegrating tablets, wet granulation

INTRODUCTION:

Oral disintegrating tablets are also called as 'mouth dissolving tablets', 'orodispersible tablets', quick disintegrating tablets, rapid dissolving tablets, porous tablets and rapimelts[1].

VARIOUS TECHNOLOGIES USED IN THE MANUFACTURE OF ODT:

The performance of ODT depends on the technology used in their manufacture. The orally disintegrating property of the tablet is attributable to a quick ingress of water into the tablet matrix, which creates porous structure and results in rapid disintegration. Hence, the basic approaches to develop ODT include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent & using highly water-soluble excipients in the formulation[4]. Following technologies have been used by various researchers to prepare ODT: -

1. Freeze-Drying or Lyophilization
2. Tablet Molding
3. Spray Drying
4. Sublimation
5. Direct Compression
6. Cotton Candy Process
7. Mass-Extrusion
8. Determination of disintegration time of ODTs:
9. *In vitro* Determination of Disintegration Time:
10. *In vivo* Determination of Disintegration Time of ODTs:

In vivo disintegration tests of ODTs can be conducted on volunteers who are usually randomized to receive the treatments and then directed to clean their mouths with water[33]. Tablets are placed on their tongues, and the time for disintegration is measured by immediately starting a stopwatch. The volunteers are allowed to move FDTs against the upper roof of the mouth with their tongue and to cause a gentle tumbling action on the tablet without biting on it or tumbling

it from side to side. Immediately after the last noticeable granule has disintegrated, the stopwatch is stopped and the time recorded.

OBJECTIVES AND PLAN OF WORK:

1. To prepare orally disintegrating tablet formulation of Chlorpheniramine maleate by wet granulation, direct compression in order to achieve rapid disintegration time and mask the bitter taste of the drug.
2. To prepare oro dissolving films of Chlorpheniramine maleate by solvent casting method using two different polymers to achieve rapid disintegration time
3. To evaluate these Chlorpheniramine maleate formulations by invitro methods and to select the best formulation among them.
4. To assess the performance of taste masked formulation of Chlorpheniramine maleate in healthy human volunteers.

MATERIALS:

Chlorpheniramine maleate: Gift sample from Dr.Reddys, Hyderabad.; Talc: Gift sample from Euro Drug Laboratories

Vanilla flavor: Gift sample from IFF; Peppermint flavor: Gift sample from Euro Drug Laboratories; Aspartame: Gift sample from Euro Drug Laboratories

Methods:

For ODT:

- Direct Compression
- Wet Granulation

For ODF:

- Solvent Casting Method

Standard graph of Chlorpheniramine maleate drug in distilled water was plotted preparing the concentrations from 2 – 60 µg/ml and absorbance was checked at 263 nm. An excellent correlation coefficient (R^2=0.9998) was observed (**Table 15, Fig 4**)

Table 16: Physical parameters for the final blend

Formulation	Angle of Repose		Compressibility index		Hausner Ratio		Friability in %	
	W.G	D.C	W.G	D.C	W.G	D.C	W.G	D.C
Polyplasdone XL4	29°.7”	28°.2”	12.3	13.8	1.15	0.98	0.78	0.73
Polyplasdone XL6	28°.6”	29°.9”	15.9	14.6	1.19	1.08	0.83	0.84
Polyplasdone XL8	29°.4”	29°.1”	12.8	13.1	1.13	1.16	0.89	0.91
Ac-di-sol 4	28°.1”	25°.6”	15.7	12.6	1.17	0.99	0.71	0.83
Ac-di-sol 6	28°.4”	27°.3”	12.4	14.9	1.14	1.13	0.74	0.85
Ac-di-sol 8	27°.7”	28°.6”	11.2	13.7	1.13	1.17	0.79	0.91
Explotab 4	26°.7”	26°.9”	12.3	14.3	1.18	1.06	0.77	0.85
Explotab 6	28°.7”	27°.3”	12.3	14.6	1.15	1.08	0.81	0.76
Explotab 8	29°.3”	27°.5”	15.9	15.1	1.19	1.14	0.82	0.84

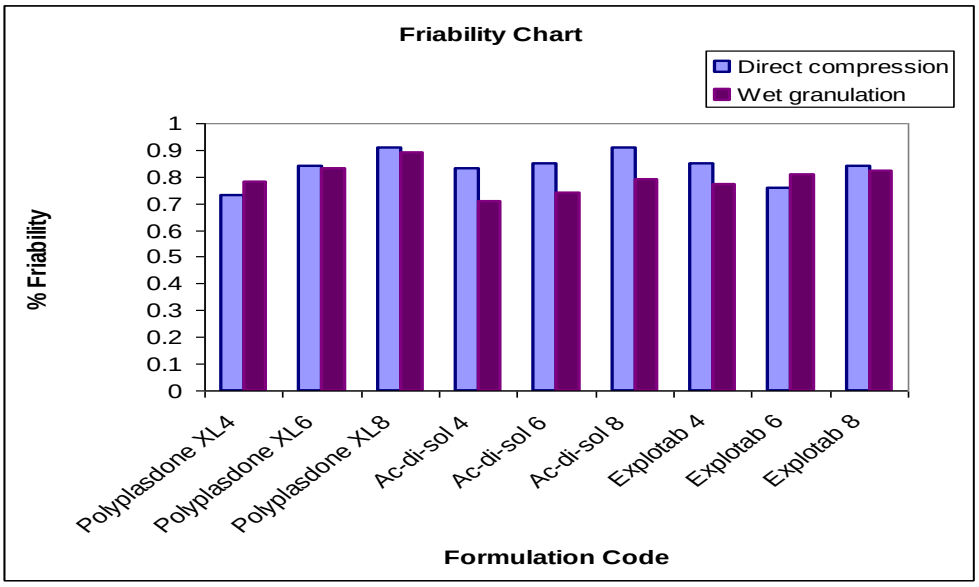

Fig. 5: Graphical representation of friability of different Chlorpheniramine maleate ODT formulations prepared by different methods

The friability for conventional tablets should be within 1% and in all the formulations which are prepared by different methods; no tablet exceeded 1% friability range (Table 16, Fig.5)

Note: W.G. – Wet granulation

D.C. – Direct compression

Table 17: Physical parameters of the compressed tablets:

Formulation	Hardness(kg/cm^2)		Thickness (mm)		Weight Variation in mg	
	W.G	D.C	W.G	D.C	W.G	D.C
Polyplasdone XL4	1.6±0.38	1.6±0.25	1.92±0.03	2.15±0.04	79.7±1.38	82±2.12
Polyplasdone XL6	1.9±0.27	2.0±0.21	1.90±0.04	1.98±0.05	77.8±1.43	81±1.52
Polyplasdone XL8	1.7±0.36	2.2±0.37	1.90±0.03	2.05±0.03	88.15±2.06	79±1.68
Ac-di-sol 4	1.9±0.21	1.8±0.46	1.94±0.02	1.94±0.03	79.00±1.56	79.15±1.38
Ac-di-sol 6	1.7±0.48	2.3±0.24	1.98±0.03	2.08±0.04	82.00±1.37	80.25±2.46
Ac-di-sol 8	1.8±0.34	2.1±0.28	1.97±0.05	2.07±0.05	81.00±1.95	79.25±3.62
Explotab 4	1.9±0.28	2.2±0.37	1.94±0.07	2.04±0.02	78.25±2.16	80.05±2.94
Explotab 6	1.6±0.23	2.1±0.28	1.92±0.06	2.02±0.04	80.25±1.82	79.05±3.96
Explotab 8	1.8±0.31	2.2±0.34	1.96±0.02	2.06±0.03	79.10±1.28	79.65±2.67

In all formulations as shown in table (17) no tablets were outside the ± 10% of tablet weight variation test and tablet thickness of all the formulations was within ±5% standard value and hardeness is within the limits of 1 to 3 kg/cm^2.

Table 18: Assay of different Chlorpheniramine maleate ODT formulations

Formulation	Amount(mg)		% Assay	
	W.G	D.C	W.G	D.C
Polyplasdone XL4	3.98	3.99	99.66	99.77
Polyplasdone XL6	3.96	3.89	99.08	97.25
Polyplasdone XL8	4.04	3.94	101.05	98.52
Ac-di-sol 4	3.97	4.04	99.25	101.00
Ac-di-sol 6	3.82	3.97	95.50	99.35
Ac-di-sol 8	3.89	4.00	97.25	100.20
Explotab 4	3.80	3.99	95.00	99.77
Explotab 6	4.02	3.82	100.05	95.50
Explotab 8	3.92	3.80	98.12	95.15

A good content uniformity was observed among all the formulations of Chlorpheniramine maleate. In case of direct compression, the range was 95.15% in Explotab 8 and 101.00% in Ac-di-sol 4. In case of wet granulation, the range was 95.00% in Explotab 4 and 101.05% in Polyplasdone XL8.

Table 19: Wetting time and water absorption ratio of different Chlorpheniramine maleate ODT formulations by different methods

Formulation Code	Wet granulation		Direct compression	
	Wetting time(sec)	Water absorption ratio(R)	Wetting time(sec)	Water absorption ratio(R)
Polyplasdone XL4	38	98.5	18	99.5
Polyplasdone XL6	36	101.9	16	103
Polyplasdone XL8	33	111.9	15	126
Ac-di-sol 4	56	122.4	36	129
Ac-di-sol 6	50	135.5	28	141
Ac-di-sol 8	40	150	24	145.2
Explotab 4	80	95	48	94
Explotab 6	52	95.5	26	96.3
Explotab 8	43	122.4	24	98.2

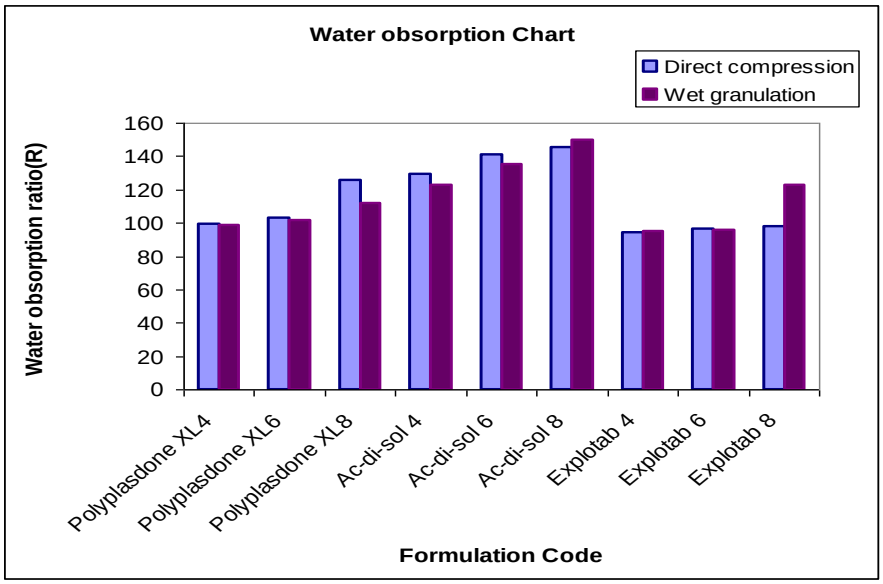

Fig. 6: Graphical representation of water absorption ratios of different Chlorpheniramine maleate ODT formulations by different methods

Wetting time was determined for all the formulations but the results obtained could not be correlated with any of the other parameters related to ODTs as in case of Chlorpheniramine maleate. The varied wetting time for different formulations may be due to the changes in the compressional pressures, which could not be controlled during the production of tablets (Table 19). Water absorption ratio (R) value increased with increase in the superdisintegrant concentration (from 4-8 %). There existed a direct relationship for each of Chlorpheniramine maleate ODT formulations. This increase is due to the water up taking ability of the superdisintegrants. More is the superdisintegrant concentration, greater is the water up take and thereby increase in the 'R' value is observed. This pattern followed in case of all the 3 superdisintegrants used in wetgranulation method and direct compression method.

Table 20: Disintegration time of Chlorpheniramine maleate ODT formulations obtained by different methods

Formulation Code	Disintegration time(sec)	
	Wet granulation	Direct compression
Polyplasdone XL4	42	22
Polyplasdone XL6	38	20
Polyplasdone XL8	35	18
Ac-di-sol 4	60	38
Ac-di-sol 6	50	30
Ac-di-sol 8	46	26
Explotab 4	78	53
Explotab 6	65	46
Explotab 8	54	40

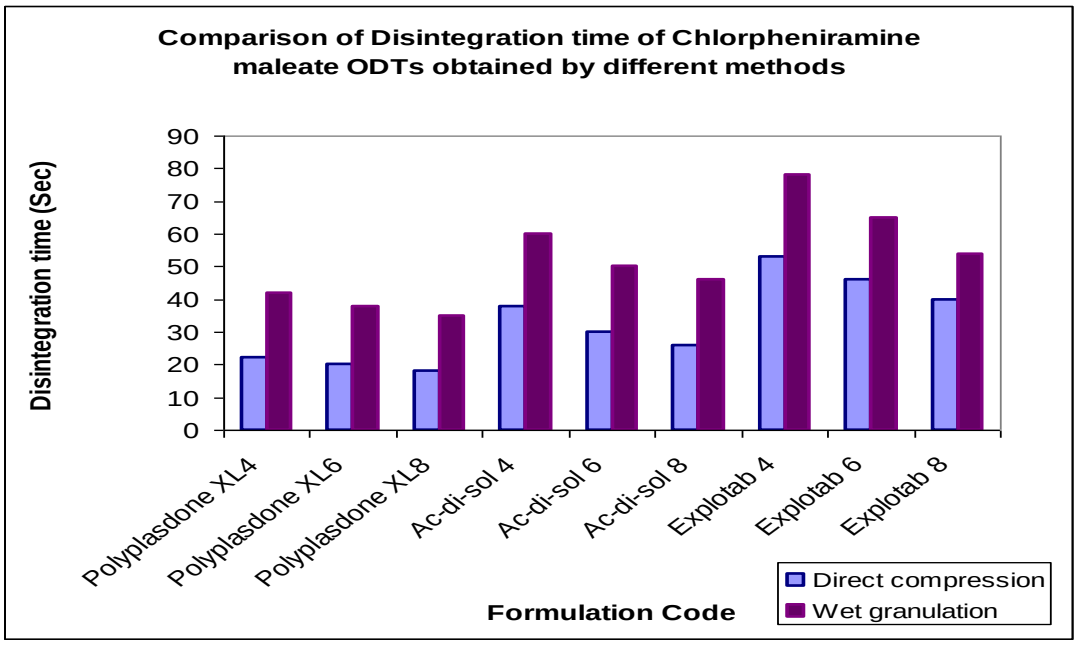

Fig. 7: Comparison of Disintegration time of Chlorpheniramine maleate ODTs obtained by different method

Disintegration time was given the major importance in selection of the best ODT formulation among all the formulations. For all the formulations, with increase in the superdisintegrant concentration from 4-8%, the disintegration time decreased accordingly (Table 20). Edward stated that wicking and capillary action are postulated to be major factors in the ability of these superdisintegrants to be function.

But the tablets prepared with explotab as a superdisintegrant took more time to disintegrate than other superdisintegrants may be due to the purity of the superdisintegrant.

The tablets containing Polyplasdone exhibit quick disintegration time followed by tablets containing Ac-di-sol and Explotab. The probable reason for delayed disintegration and wetting of the tablets might be slow water uptake or more gelling tendency of the Ac-di-sol and explotab.

From above results PP XL 8 was selected as the best ODT formulation among all the Chlorpheniramine maleate formulations prepared by direct compression and wet granulation.

The time for an ODT to disintegrate in the oral cavity also varies by product and the method of manufacturing.

Chlorpheniramine maleate ODT formulations prepared by wet granulation method take more time to disintegrate than tablets prepared by direct compression method.

Table 21: Water absorption ratio(R) vs Disintegration time (sec)-Correlation

Formulation code	Correlation-coefficient (R^2)	
	Direct compression	Wet granulation
Polyplasdone XL	0.8951	0.8312
Ac-di-sol	0.8942	0.9621
Explotab	0.976	0.9766

When 'R' values of each superdisintegrant formulations prepared by direct compression and wet granulation were correlated with disintegration time of those formulations, a very good correlation was obtained and a reciprocal or an inverse relationship was observed between these two parameters. Increase in the 'R' value exhibited lower disintegration times (Table 21).

Cumulative % of Drug release from Chlorpheniramine maleate ODT formulations

Table 22: Cumulative Percent Release of Chlorpheniramine maleate -C. P

Time (min)	Cumulative Percent Release of Chlorpheniramine maleate					
	Polyplasdone XL 4		Polyplasdone XL 6		Polyplasdone XL 8	
	W.G	D.C	W.G	D.C	W.G	D.C
1	39.5±1.24	46.02±2.48	46.02±2.46	59.75±3.52	59.2±1.37	86.55±1.62
3	46.01±1.67	89.2±2.67	58.1±3.08	90.6±2.78	68.6±1.42	96.15±1.94
5	62.6±1.53	99.5±2.92	78.2±2.93	100.2±2.42	84.3±1.28	100.2±1.43
10	77.7±1.38	99.62±1.96	89.1±3.08	99.5±3.16	90.1±1.82	99.5±2.07
15	90.2±0.97	99.62±2.43	95.6±3.67	100.2±2.91	97.3±1.97	99.5±1.95
20	95.4±1.72	99.61±2.43	98.7±2.76	100.1±2.91	99.98±2.16	99.6±1.95
30	99.9±1.63	99.63±2.43	99.98±2.13	100.1±2.91	99.99±1.52	99.5±1.95

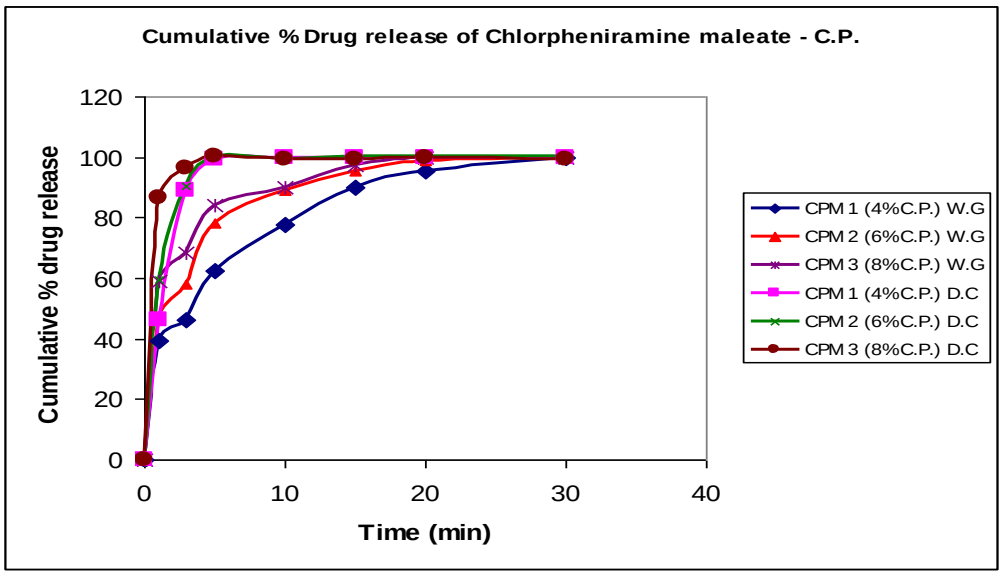

Fig:8: **Cumulative Percent Release of Chlorpheniramine maleate**

Note: C.P. – Cross Povidone (Polyplasdone XL)

Table 23: Cumulative Percent Release of Chlorpheniramine maleate -CCS

TIME (min)	Ac-di–sol4		Ac-di-sol6		Ac-di–sol8	
	W.G	D.C	W.G	D.C	W.G	D.C
1	39.1±4.15	40.52±2.48	45.5±2.46	59.75±2.12	59.5±3.37	60.44±2.62
3	43.05±3.81	71.43±3.17	60.3±3.08	83.1±3.78	67.3±2.28	86.54±2.94
5	60.6±3.18	101.65±2.06	77.9±2.83	100.27±3.42	83.4±2.64	101.65±3.43
10	77.2±3.38	100.96±1.96	89.3±2.08	100.96±3.16	92.1±1.32	102.34±2.17
15	90±4.29	100.96±3.30	95.82±1.95	100.96±2.91	96.9±1.37	101.65±2.45
20	92.3±2.09	100.95±3.30	96.34±2.86	100.95±2.91	98.89±2.97	101.64±2.45
30	98.5±2.38	100.94±3.30	99.54±3.13	100.96±2.91	100.4±1.92	101.62±2.45

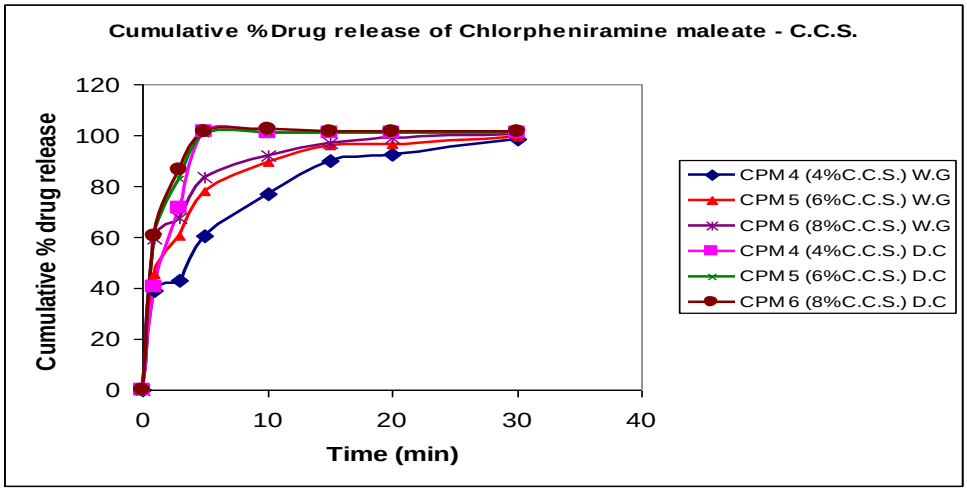

Fig 9: Cumulative Percent Release of Chlorpheniramine maleate –CCS

Note: C.C.S. – Cross Carmelose Sodium (Ac-di–sol)

Table 24: Cumulative Percent Release of Chlorpheniramine maleate -SSG

TIME (min)	Explotab4		Explotab6		Explotab8	
	W.G	D.C	W.G	D.C	W.G	D.C
1	28.2±2.41	32.97±2.21	31.2±3.61	39.84±3.32	33.3±1.42	40.52±2.62
3	35.7±2.68	78.98±1.77	39.7±3.18	83.1±3.78	41±1.66	87.23±2.48
5	51.6±1.73	86.54±1.86	55.6±2.72	94.09±3.42	60.1±2.28	96.8±3.43
10	67.8±2.38	97.27±3.96	70.7±3.48	98.9±3.16	78.2±3.82	100.93±4.07
15	75.6±1.97	98.27±4.43	82.5±3.47	99.5±1.91	88.9±4.97	100.96±2.95
20	84.2±2.77	98.25±4.43	93±3.16	99.4±1.91	96.65±2.56	100.95±2.95
30	95±3.18	98.23±4.43	97.45±4.13	99.7±1.91	100.1±3.52	100.94±2.95

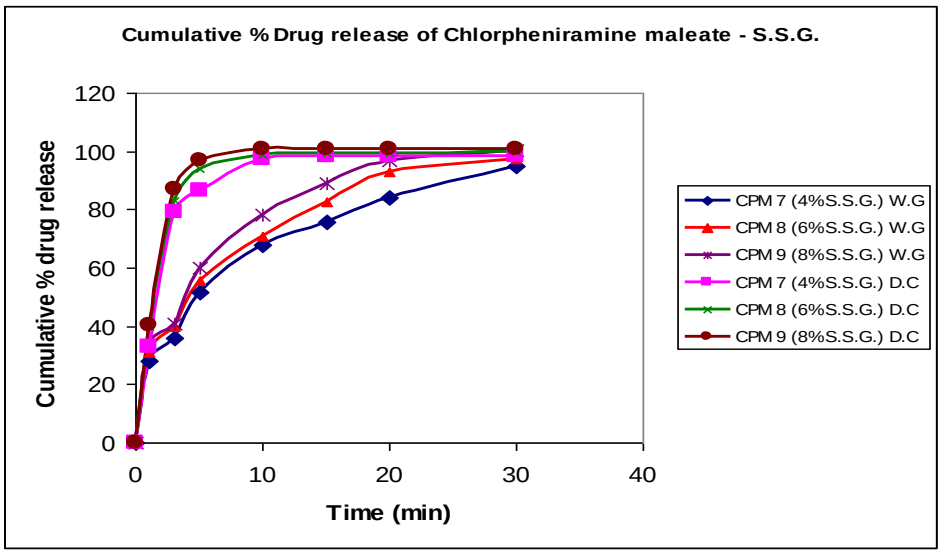

Fig10: Cumulative Percent Release of Chlorpheniramine maleate -SSG

In all formulations of PP XL and Ac-di-sol 99% of drug was released in 5 mins. But formulations containing Explotab releases the drug very slowly and in case of Explotab 8 99% drug was released in 10 mins and in case of Explotab 6 and 4 it is in 30 mins. It is may be due to purity of the super disintegrant.

Note: S.S.G. – Sodium Starch Glycolate (Explotab)
PP XL – Polyplasdone XL

Table 25: Cumulative Percent Release of Chlorpheniramine maleate using combination of super disintegrants

TIME(min)	SSG4%+CP4%		SSG4%+CCS4%	
	W.G	D.C	W.G	D.C
1	38.2±2.41	42.52±2.21	37.2±3.61	58.5±3.32
3	65.7±2.68	78.7±1.77	59.7±3.18	82.6±3.78
5	81.6±1.73	97.5±1.86	65.6±2.72	98±3.42
10	87.8±2.38	98.21±3.96	82.7±3.48	99.4±3.16
15	95.6±1.97	99.92±4.43	93.5±3.47	99.9±1.91
20	99.2±2.77	99.94±4.43	98±3.16	99.9±1.91
30	99.4±3.18	99.97±4.43	99.45±4.13	99.9±1.91

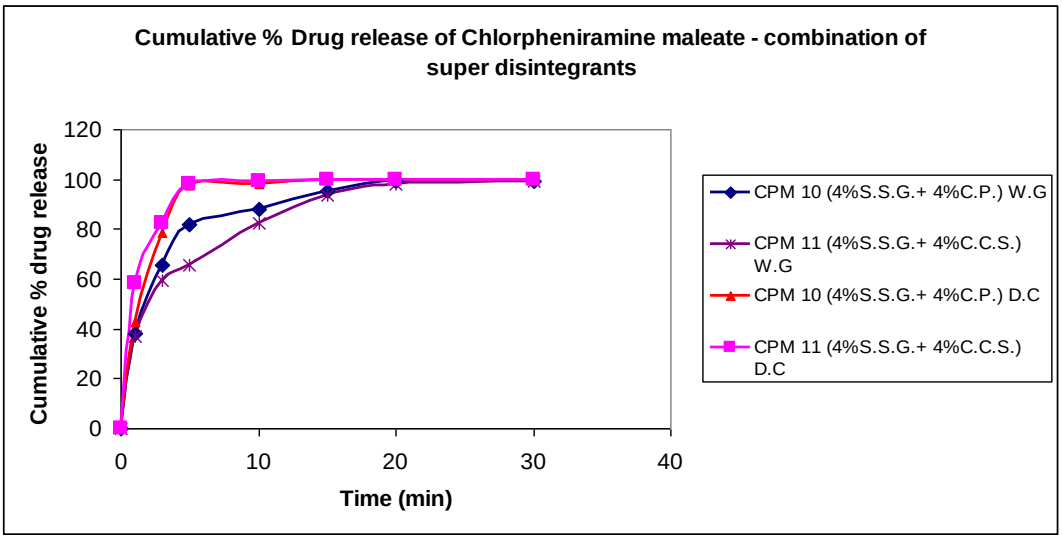

Fig11: Cumulative Percent Release of Chlorpheniramine maleate - using combination of super disintegrants

By using the combination of super disintegrants there is no synergetic action between the disintegrants but 99.9% drug release was observed within 15 mins both in case of SSG4%+CP4% and SSG4%+CCS4%.

Table 26: Cumulative % Drug release of Chlorpheniramine maleate - formulated with 0.1 % of SLS by direct compression technique

Time	% Drug Release		
	SSG 4 %	SSG 6%	SSG 8%
0	0	0	0
1	33.3	39.8	40.52
3	78.2	83.6	87.23
5	86.48	94.7	96.8
10	97.29	98.36	99.5
15	98.3	98.37	99.53

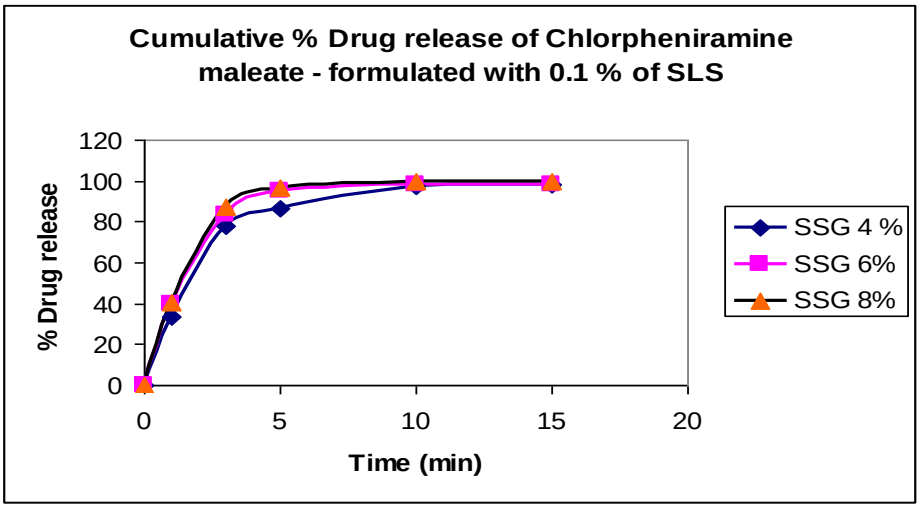

Table 27: Mean weight and Mean thickness of Chlorpheniramine maleate ODF formulations

Formulation Code	Mean weight ± SD	Mean thickness ± SD
HPMC E15 A1	22.76±2.43	0.1±0.04mm
HPMC E15 A2	35.26±3.12	0.14±0.05mm
HPMC E5 B3	42.75±2.51	0.12±0.03mm

Table 28: Mean *In vitro* and *In vivo* Disintegration time of Chlorpheniramine maleate ODF formulations

Formulation Code	Disintegration time(sec)	
	In vitro disintegration time	*In vivo* disintegration time
HPMC E15 A1	10±2.0	7±2.0
HPMC E15 A2	20±2.0	18±2.0
HPMC E5 B3	13±2.0	10±2.0

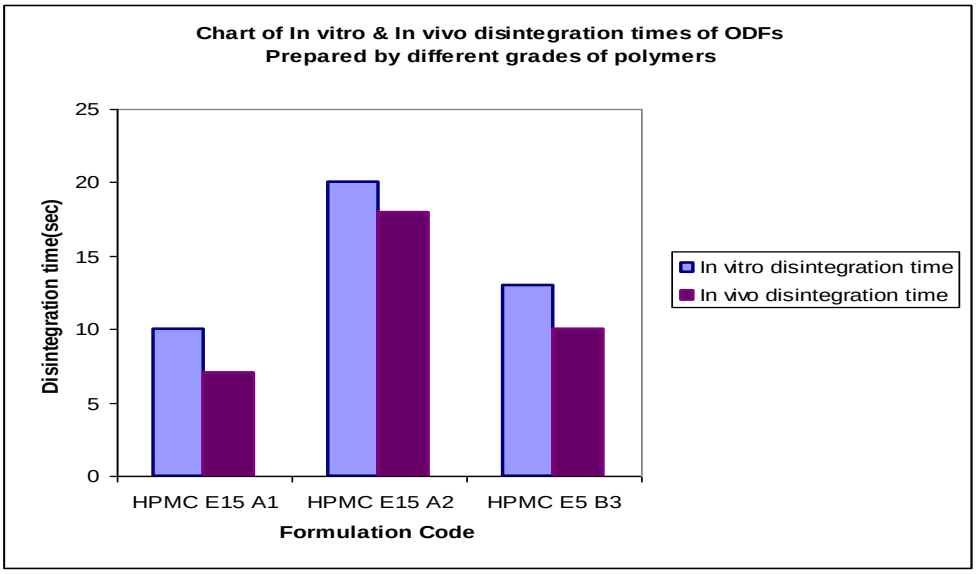

Fig13: Graphical representation of *In vitro* & *In vivo* disintegration times of ODFs

Prepared by different grades of polymers

The disintegration time of HPMC E15 A1 is less than A2 and B3. A2 has more disintegration time because of more concentration of polymer and also high viscosity grade of the polymer.

Table 29: Assay of different Chlorpheniramine maleate ODF formulations

Formulation Code	Concentration in mg	% Assay
HPMC E15 A1	3.98	99.5
HPMC E15 A2	4.28	107
HPMC E5 B3	4.02	100.5

A good content uniformity was observed among all the formulations of Chlorpheniramine maleate ODFs.

Table 30: Cumulative % Release of Chlorpheniramine maleate ODF formulations

Cumulative % Release of Chlorpheniramine maleate ODF formulations			
Time	**HPMC E15 A1**	**HPMC E15 A2**	**HPMC E5 B3**
0	0	0	0
1	87.25	83.1	85.3
3	100.9	95.2	98.9
5	103.92	102.3	99.9
7	103.65	102.1	99.92
10	103.71	102.4	99.91
15	103.72	102.7	99.93

In A1 and B3 formulations 100% drug is released within 3 mins but in A2 100% drug is released within 5 mins. Because of high viscosity and concentration of polymer, so it took time to dissolve the polymer.

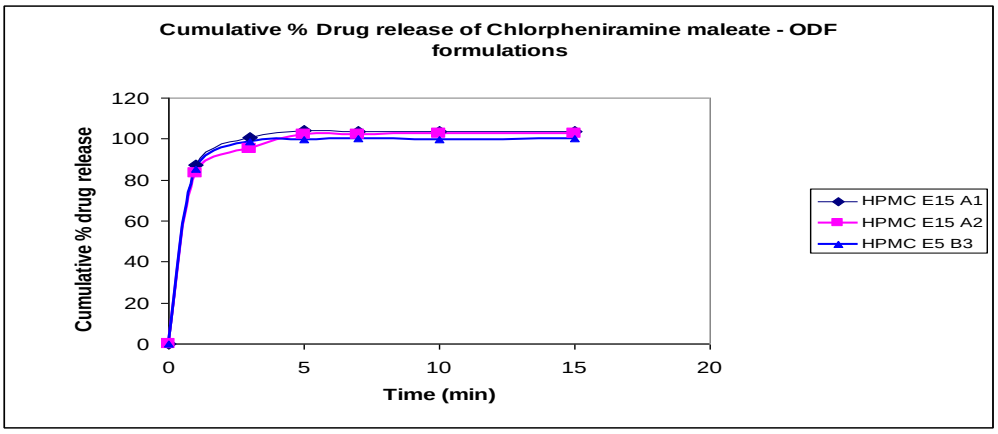

Fig14: Cumulative Percent Release of Chlorpheniramine maleate - ODF formulations

Table 31: Comparison of disintegration times of ODTs obtained by different methods and different formulation of ODFs

	Disintegration time(sec)	
Formulation Code	**Wet granulation**	**Direct compression**
Polyplasdone XL4	42	22
Polyplasdone XL6	38	20
Polyplasdone XL8	35	18
Ac-di-sol 4	48	38
Ac-di-sol 6	44	30
Ac-di-sol 8	40	26
Explotab 4	83	63
Explotab 6	66	56
Explotab 8	55	48
	In vitro	***In vivo***
HPMC E15 A1	10	7
HPMC E15 A2	20	18
HPMC E5 B3	13	10

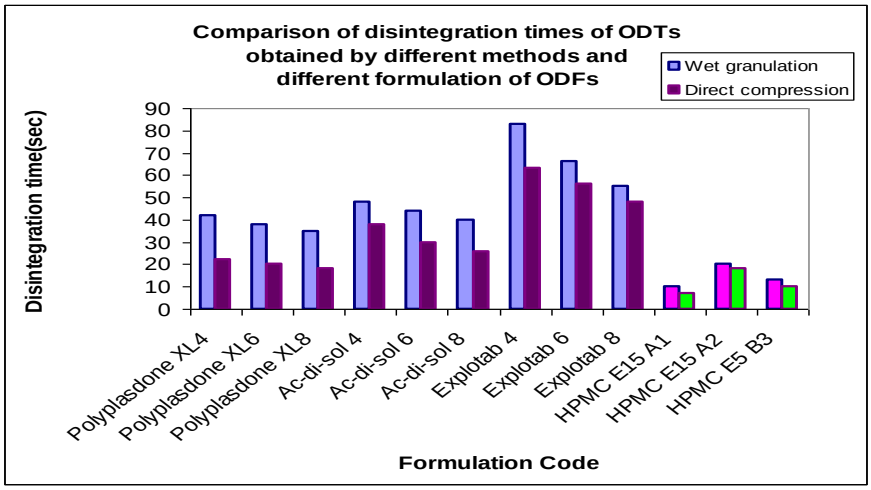

Fig15: Comparison of disintegration times of ODTs obtained by different methods and different formulation of ODFs

By above results we can conclude that ODFs has less disintegration time i.e. within 10 mins than ODT formulations.

Table 32: Comparison of Dissolution profile of Chlorpheniramine maleate ODT formulations obtained by different methods using Polyplasdone 8% & ODF formulations obtained by different concentrations of polymers

	Chlorpheniramine maleate ODT			Chlorpheniramine maleate ODF		
Time	8% C.P (WG)	8% C.P (DC)	SSG 4% + CCS 4%	HPMC E15 A1	HPMC E15 A2	HPMC E5 B3
0	0	0	0	0	0	0
1	59.2±1.37	86.55±1.62	58.5±3.32	87.25	83.1	85.3
3	68.6±1.42	96.15±1.94	82.6±3.78	100.9	95.2	98.9
5	84.3±1.28	100.2±1.43	98±3.42	103.92	102.3	99.9
10	90.1±1.82	99.5±2.07	99.4±3.16	103.71	102.4	99.91
15	97.3±1.97	99.5±1.95	99.9±1.91	103.72	102.7	99.93
20	99.98±2.16	99.6±1.95	99.9±1.91	-	-	-
30	99.99±1.52	99.5±1.95	99.9±1.91	-	-	-

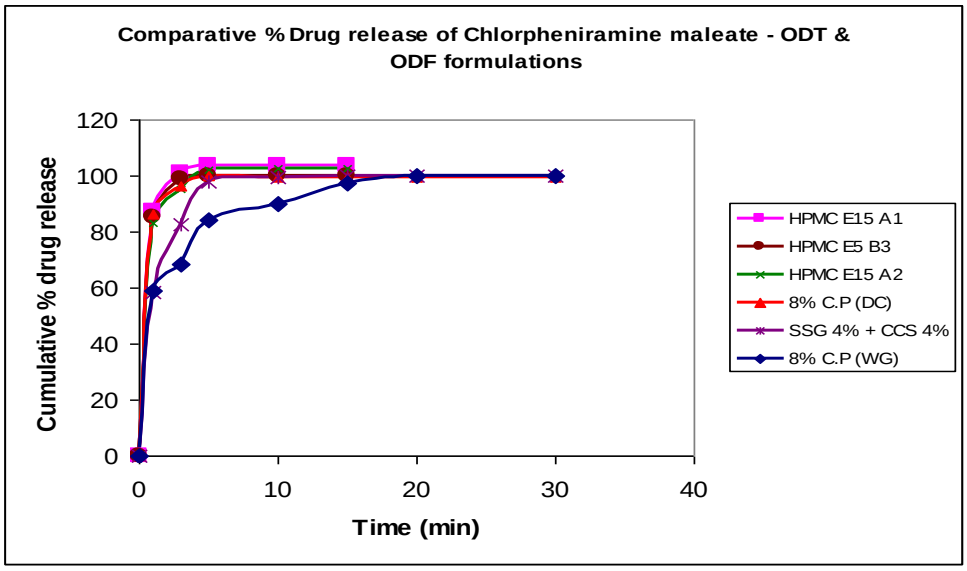

Fig16: Comparison of % Drug release of Chlorpheniramine maleate – ODT & ODF formulations

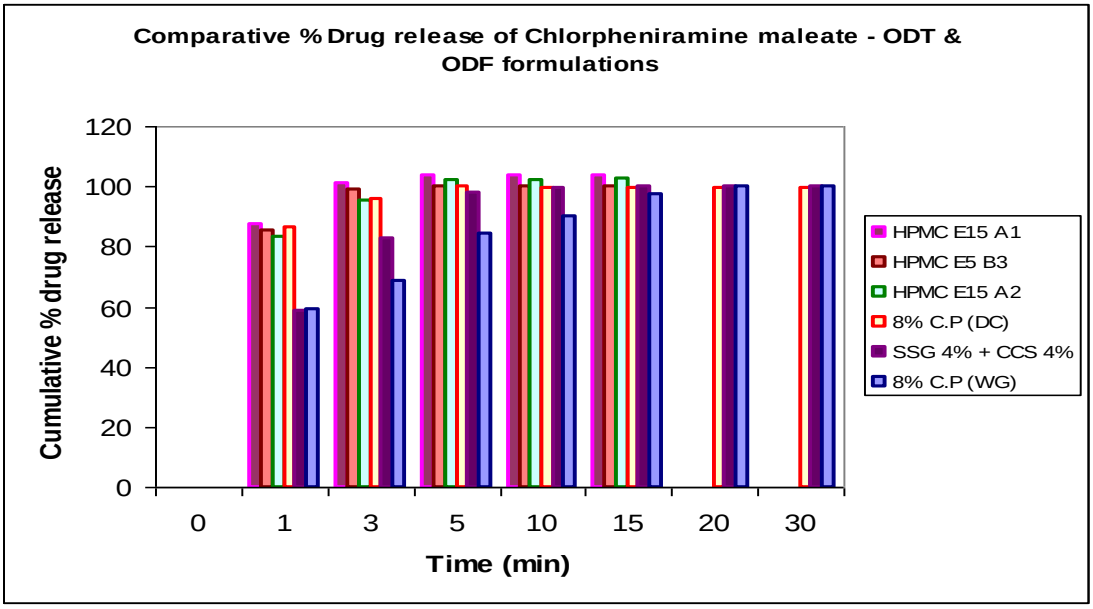

Fig17: Comparison of Dissolution profile of Chlorpheniramine maleate ODT formulations obtained by different methods using Polyplasdone 8% & ODF formulations obtained by different concentrations of polymers

The rapid drug dissolution observed for direct compression than wet granulation, it may be due to easy breakdown of particles and rapid absorption of drug into the dissolution medium. Based on the above results the tablets prepared with wet granulation take more time to release the drug than direct compression. In all the formulations, with increase in the concentration of super disintegrant the cumulative % drug release increased, 99% of drug released in 5 min in case of direct compression technique, and in case of ODFs 99% drug released in 3 min, but wet granulation takes more time to release the drug. Because ODFs are thin film with more surface area they get wet quickly and disintegrate then dissolve faster than ODTs.

CONCLUSIONS:

- Of three superdisintegrants Polyplasdone XL showed better performance in disintegration time when compared to Ac-di-sol and Explotab in case of Chlorpheniramine maleate ODT. Order of the superdisintegratnt activity is as follows:
- Polyplasdone XL> Ac-di-sol > Explotab
- Based on the disintegration results direct compression techniques were more efficient than wet granulation technique. So that wet granulation technique not suitable for preparation of orally disintegrating tablets.
- The formulations of Polyplasdone XL 8 was found to be the best among Chlorpheniramine maleate ODT formulations which were prepared by wet granulation and direct compression because it has exhibited faster disintegration time when compared to other formulations.
- Based on the disintegration results and dissolution studies ODFs have faster disintegration time and drug releases faster than ODT formulation of Polyplasdone XL 8 i.e., with in 3 mins. So ODFs are best formulations than ODT formulations.
- Of the ODFs formulations HPMC E15 A1 and HPMC E5 B3 has less disintegration time and compare to HPMC E15 A2 and HPMC E15 A1 has still less disintegration time than HPMC E5 B3. So ODF formulated with HPMC E15 A1 is best formulation.
- The bitter taste of the drug was masked by Aspartame, peppermint flavor and Vanilla flavor.

REFERENCES:

1. Parakh S.R, Gothoskar A.V: A review of mouth dissolving tablet technologies. Pharm. Tech., 27(11): 92-98, (2003).
2. Jaccard T.T, Leyder J: Une Nouvelle Forme Galenique: Le Lyoc. Ann. Pharm.Fr., 43(2): 123-131, 1985.

3. Remon J.P, Corveleyn S: Freeze – Dried Disintegrating Tablets. US Patent 6,010,719, (2000). News Release, Scherer Announces Launch of First U.S. Product Using Zydis® Technology September, (1996).
4. Gregory G.K.E, HoD: Pharmaceutical Dosage Form Packages. US Patent 4,305,502, (1981).
5. Yarwood R: Zydis – A novel, Fast Dissolving Dosage Form. Man. Chem., 61: 36-37, (1990).
6. Seager H: Drug Delivery Products and the Zydis Fast- Dissolving Dosage Form. J. Pharm. Pharmacol., 50(4): 375-385, (1998).
7. Van Scoik K.G: Solid pharmaceutical dosage in tablet triturate form and method of producing same. US Patent 5,082,667, (1992).
8. Masaki K: Intrabuccally Disintegrating Preparation and Production Thereof. US patent: 5,466,464, (1995).
9. Indurwade N.H, Rajyaguru T.H, Nakhat P.D: Novel Approach – Fast Dissolving Tablets. Indian Drugs, 39 (8), (2002)
10. Allen L.V, Wang B: Method of making a rapidly dissolving tablet. US Patent No. 5,635,210, (1997).
11. Allen L.V, Wang B: Rapidly Dissolving Tablets. US Patent No. 5,807,576, (1998).
12. Heinemann H, Rothe W: Preparation of porous tablets. US Patent No. 3,885,026, (1975).
13. Knitsch K.W: Production of porous tablets. US Patent No. 4,134,943, (1979).
14. Makino T, Yamada M, Kikuta J.I: Fast dissolving tablet and its production. US Patent No. 5,720,974, (1998).
15. Bi Y: Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity. Chem. Pharm. Bull., 44 (11): 2121-2127, (1996).
16. Watanabe Y: New compressed tablet rapidly disintegrating in saliva in the mouth using crystalline cellulose and a disintegrant. Biol. Pharm. Bull., 18 (9): 1308-1310, (1995).
17. Wehling F, Shuehle S, Madamala N: Effervescent dosage form with microparticles. US Patent No. 5,178,878, (1993).
18. Kaushik D, Dureja H, Saini T. R: Mouth Dissolving Tablets: A review. Indian Drugs, 41(4): 187-193, (2004).
19. Michaelson J: Rapidly Disintegrable Tablet Composition and Method. US Patent No. 4,414,198, (1983).
20. Shirwaikar A.A: Fast Disintegrating Tablets of Atenolol by Dry Granulation Method. Ind. J. Pharm. Sci., 66(4): 422-426, (2004).
21. Fuisz R.C: Rapidly dissoluble medicinal dosage unit and method of manufacture. US Patent No. 4,855,326, (1989).
22. Morita Y, Tsuhima Y, Yasui M, Termoz R, Ajioka J, Takayam K. Evaluation of the disintegration time of rapidly disintegrating tablets via a novel method utilizing CCD camera. Chem. Pharm. Bull,.50(9),1181-1186(2002).
23. Nazaraki R, Harada T, Takami N, Kato Y, Ohwaki T. A new method for disintegration studies of rapid disintegrating tablet. Chem Pharm Bull,.52(6): 704-707, (2002).
24. Myers G.L, Battist G.E, Fuisz R.C: Process and apparatus for making rapidly dissolving dosage units and product therefrom. US Patent No. 5,866,163, (1999).
25. Misra T.K, Currington J.W, Kamath S.A, Sanghvi P.P, Sisak J.R, Raiden M.G: US Patent No. 5,869,098, (1999).
26. Mizumoto T, Masuda Y, Kukui M. US Patent No. 5,576,014, (1996).

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