ISSN 0975-6299

Vol 2/Issue 2/Apr-Jun 2011

International Journal of Pharma and Bio Sciences

RESEARCH ARTICLE

PHARMACEUTICS

FORMULATION, DESIGN AND EVALUATION OF ORALLY DISINTEGRATING TABLETS OF LORATADINE USING DIRECT COMPRESSION PROCESS

JAYADEV PATIL[1], CHANDRASEKHAR KADAM[2], VISHWAJITH V[2] AND GOPAL.V* [2]

1. Dept of Pharmacy, PRIST University, Thanjavur-613403, India.
2. College of Pharmacy, Mother Theresa Institute of Health Sciences, Indira Nagar, Puducherry-605 006, India.

GOPAL.V
College of Pharmacy, Mother Theresa Institute of Health Sciences, Indira Nagar, Puducherry-605 006, India.

ABSTRACT

The present work aims to formulate and design orally disintegrating tablets containing antihistamines like Loratadine using different pharmaceutical compositions with simple manufacturing procedures to enhance patient compliance. Loratadine was formulated into orally disintegrating tablets by direct compression method using suitable excipients like Maltodextrin, Mannitol, Micro crystalline cellulose, combination of Mannitol with Starch, Croscarmellose sodium, Citric acid, Sodium bicarbonate along with Mint flavor, which were evaluated by using simple analytical techniques. The taste of the formulation was enhanced using artificial sweetener Aspartame and Mint flavour. The tablets were evaluated for weight variation, hardness, friability, drug content, wetting time and disintegration time along with *in-vitro* dissolution. It was observed that the direct compression process using commercial grades of excipients like combination of Mannitol with Starch and Micro crystalline cellulose as directly compressible diluents along with super disintegrants like Croscarmellose Sodium was found to be more promising to prepare orally disintegrating tablets.

ISSN 0975-6299 Vol 2/Issue 2/Apr-Jun 2011

KEY WORDS

Antihistamines, Loratadine, Mannitol, Pearlitol flash, orally disintegrating tablets, direct compression.

INTRODUCTION

Tablet is the most widely used dosage form because of its convenience in terms of self administration, compactness and ease in manufacturing. Patients often experience difficulty in swallowing conventional tablets when water is not available nearby. Furthermore, pediatric and geriatric patients may also feel the inconvenience of swallowing because of under developed and degenerating nervous systems[1] respectively. Researchers have formulated ODT for various categories of drugs, which are used for therapy in which rapid peak plasma concentration is required to achieve desired pharmacological response. These include neuroleptics, cardiovascular agents, antihistamines and analgesics.

Orally disintegrating tablets are synonyms with fast dissolving tablet, mouth dispersible tablet, melt in mouth tablet, rapimelt, porous tablet or rapidly disintegrating tablet. Orally disintegrating tablets are tailor made for these patients as they immediately release the active drug, when placed on the tongue, by rapid disintegration, followed by dissolution of the drug. European pharmacopoeia[2] defines “Orodispersible tablets are uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed”. Orodispersible tablets disintegrate within 3 minutes. Orally disintegrating tablets combine the advantage of both liquid and conventional tablet formulations allowing the ease of swallowing the drug in the form of liquid dosage form. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. The main purpose of this work is only to improve patient compliance without compromising the therapeutic efficacy.

The performance of ODT depends on the technology used in their manufacture. The orally disintegrating property of the tablet is attributable to a quick intake of water into the tablet matrix, which creates porous structures and result in rapid disintegration. Hence the basic approaches to develop ODT include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water soluble excipients in the formulation. To name a few technologies used by researchers to prepare the ODT can be mentioned here like Freeze drying (Lyophilization), tablet molding, spray drying, sublimation, direct compression, cotton candy process and mass extrusion.

In the present study the direct compression method was adopted to manufacture the ODT tablets, since it is very simple and do not require any sophisticated equipments. The direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique has been applied to prepare ODT formulation because of the availability of improved excipients especially superdisintegrants like Croscarmellose sodium, directly compressible diluents, sweeteners and flavoring agents.

Super disintegrants in direct compression process have greater direct impact on rate of disintegration and dissolution of tablets. The presence of other formulation ingredients such as water- soluble excipients and effervescent agents further hastens the process of disintegration. Watanabe et al[3] have used microcrystalline cellulose (MCC) and low substituted hydroxyl propyl cellulose (HPC) to

manufacture ODT. The ratio of MCC to HPC varied from 8:2 to 9:1.

Ito and Sugihara[4] investigated use of agar powder as a disintegrant because the powder absorbs water and swells without forming gel at physiological temperature. Ethypharm (France) has introduced a Flash- dose technology, which contains coated crystals and micro granules along with the disintegrants. In this technology, two types of granules are used; a disintegrating agent (e.g. modified cellulose- Croscarmellose) which has a high swelling force, and a swelling agent (e.g. starch) which has a low swelling force.

The bases of Orasolv[5] technology in US Patent assigned to Cima Labs have also developed effervescent tablets in which disintegration is aided by evolution of carbon dioxide.

Saliva activates the effervescent agent, causing the tablet to disintegrate. Second-generation technology developed by Cima Labs is the Durasolv technology used for the production of robust, mouth dissolving tablets. Care should be observed because effervescent excipients and final product require higher protection against humidity conditions.

Shirwaikar and coworkers[6] prepared Atenolol tablets by dry granulation method using three super disintegrants, Croscarmellose sodium (Ac-Di-Sol), Crosspovidone and Sodium starch glycolate and they found that Ac-Di-Sol was the best super disintegrant among the three.

Sugar Based Excipients[7-11]: This is another approach to manufacture ODT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouth feel.

Mizumito et al[12] have classified sugar-based excipients into two types on the basis of molding and dissolution rate. Type 1 saccharides (lactose and mannitol) exhibit low moldability but high dissolution rate.

Type 2 saccharides (maltose and maltilol) exhibit high moldability and low dissolution rate. Moldability is defined as the capacity of the compound to be compressed or molded. The mold ability of type 1 saccharide can be improved by granulating it with type 2 saccharides. WOWTAB technology used in Benadryl fast melt tablets uses this technique. Most commercial ODTs have been developed using mannitol as the bulk excipient of choice. Mannitol is overwhelmingly preferred over lactose because of its extremely low hygroscopicity, excellent chemical and physical compatibility, good compressibility and better sweetness. ODT formulators prefer to use a directly compressible mannitol, which enables the preparation of robust tablets that can withstand processing and transportation. Specially textured directly compressible, spray-dried, or granulated mannitol excipients have been designed to meet these needs. These excipients under defined manufacturing conditions gives a highly porous structure and friable exterior structure which helps in faster disintegration of ODT, they also provide a satisfactory mouth feel and so suitable for use in preparation of harder ODT by direct compression at low pressure[13].

Oral films and wafers are the newer technologies in the manufacturing of orally disintegrating dosage forms. They are thin elegant films of edible water-soluble polymers of various sizes and shapes like square, rectangle or disc. The strips may be flexible or brittle, opaque or transparent. They are designed to provide rapid disintegration on the tongue without the need for water. They have the advantage of a large specific surface area for disintegration. One or a combination of the following processes like hot-melt extrusion, solid dispersion extrusion, rolling and solvent casting are used to manufacture these films. A major limitation of these dosage forms is low

drug loading capacity and limited taste masking option[14].
In present study the direct compression method was adopted to manufacture the ODT tablets, since it is very simple and do not require any sophisticated equipments. The direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to prepare the ODT formulation because of the availability of improved excipients especially super disintegrants and sugar based excipients.

MATERIALS AND METHODS

Loratadine (micronised) was received from Rolabo SL, Micro crystalline cellulose (FMC Biopolymers), Pearlitol 200SD and Pearlitol flash (Roquette), Croscarmellose Sodium (Ac-Di –Sol SD-711) from FMC Biopolymers , Starch 1500 LM (Colorcon), Maltodextrin like Glucidex IT 12 (Roquette), Citric acid, Sodium bicarbonate, Colloidal silicon dioxide, Aspartame, Mint flavour, Sodium stearyl fumarate were of pharmaceutical grade.

Instruments:

1. A rotary compression machine from Kambert with 8 stations was used to prepare tablets.
2. A Mettler Toledo DSC1 Star System instrument was used for Preformulation studies.
3. An Electrolab EF-2 Friabilator USP was used to check the friability of tablets.
4. Dr.Schleuniger hardness tester was used to check the hardness of the tablets.
5. LABINDIA DISSO2000 USP to study the *in-vitro* dissolution profile.
6. Electrolab disintegration apparatus USP (Electrolab ED-2L) was used to check the disintegration time of tablets.
7. A Shimadzu model 1700 double beam UV/Visible spectrophotometer with 1cm matched quartz cells was used to measure the absorbance of samples for testing Assay and Dissolution

PREPARATION OF LORATADINE ORALLY DISINTEGRATING TABLETS:

The orally dispersible tablet of Loratadine was prepared using Micro crystalline cellulose as diluent and binder, Pearlitol 200SD as directly compressible diluent, Croscarmellose Sodium as super disintegrant and Starch 1500LM as binder and disintegrant, Maltodextrin (Glucidex IT 12) as diluent, Citric acid as salivating agent, Colloidal silicon dioxide as glidant, Aspartame as sweetener, Mint flavour as flavouring agent, Sodium stearyl fumarate as lubricant.(Table 1).

All ingredients except Colloidal silicon dioxide, Aspartame, Mint flavour, Sodium stearyl fumarate were sifted and mixed in an octagonal blender for 15 minutes. Aspartame, Mint flavour and Colloidal silicon dioxide were sifted and added to above blend and mixed for 5 minutes.
Finally the blend was lubricated using Sodium stearyl fumarate and compressed by using 8 mm flat punches with breakline on upper punch and plain on lower punch in Kambert eight station rotary compression machine to produce ODT tablets.

Table 1

Ingredients	Quantity Per Tablet (mg)								
	Trial 001	Trial 002	Trial 003	Trial 004	Trial 005	Trial 006	Trial 007	Trial 008	Trial 009
Loratadine (Micronised)	10	10	10	10	10	10	10	10	10
Pearlitol flash	----	----	----	----	----	----	----	----	103
Mannitol (Pearlitol 200SD)	50	50	55	55	----	40	40	40	----
Maltodextrin (Glucidex IT 12)	----	----	----	----	55	20	20	----	----
Micro crystalline cellulose (Avicel-102)	78.6	77	77.5	78	77.5	79	76.5	89.5	20
Croscarmellose Sodium (Ac-Di-Sol SD-711)	12	12	12	12	12	12	12	12	15
Sodium bicarbonate	----	----	----	----	----	----	----	----	6
Starch 1500 LM	7	7	7	7	7	----	----	7	----
Citric acid (Anhydrous)	3	1.5	0.5	----	0.5	0.5	0.5	1	3
Colloidal silicon dioxide	2	3	2	2	2	2	3	3	5.2
Strawberry Flavour	----	----	----	----	----	----	----	----	1
Aspartame	4	2	2	2	2	2	2	2	4.8
Mint flavor	0.4	0.5	0.5	0.5	0.5	0.5	0.5	0.5	----
Lubrication									
Sodium stearyl fumarate	3	7	3.5	3.5	3.5	3.5	5	5	2
Tablet weight (mg)	**170**	**170**	**170**	**170**	**170**	**170**	**170**	**170**	**170**

Preformulation studies:

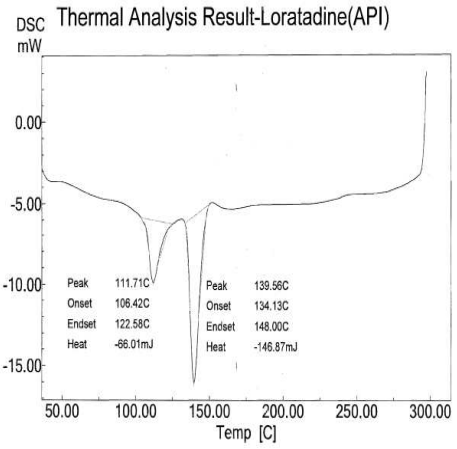
Loratadine along with different excipients (Table 2) were subjected to accelerated stress conditions after preparing the drug and excipients admixtures and evaluated by using Differential scanning colorimeter (Mettler Toledo DSC1 Star System). The drug- excipients ratios will vary for diluents, disintegrants, binders, lubricants and sweeteners present in the formulation. Results indicated that there was no incompatibility of following excipients with Loratadine (Figure 1).

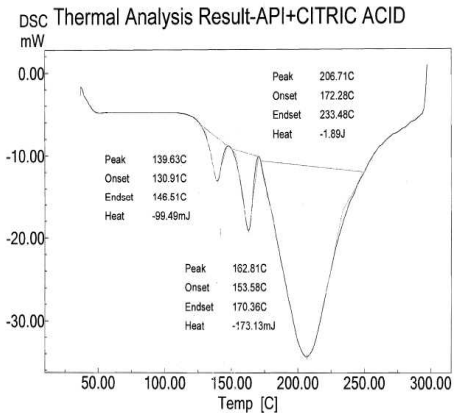
Table 2

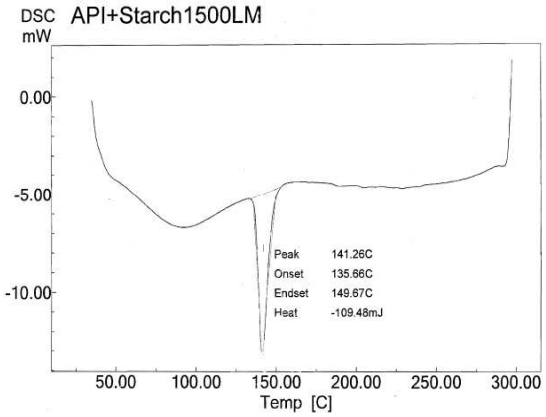
Preformulation study:

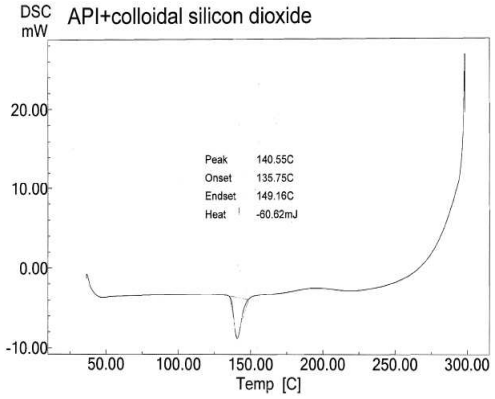
SLNo	INGREDIENTS	RATIO	QUANTITY TAKEN (g)
1	Loratadine (API)	1:0	1
2	API + Mannitol	1:5	0.5 + 2.5
3	API +Croscarmellose sodium (Ac-di-sol SD-711)	1:5	0.5 + 2.5
4	API + Starch 1500 LM	1:0.5	1 + 0.5
5	API + Maltodextrin (Glucidex IT-12)	1:0.5	1 + 0.5
6	API + Citric acid	1:0.25	1 + 0.25
7	API + Colloidal silicon dioxide (Aerosil)	1:0.25	1 + 0.25
8	API + Aspartame	1:0.25	1 + 0.25

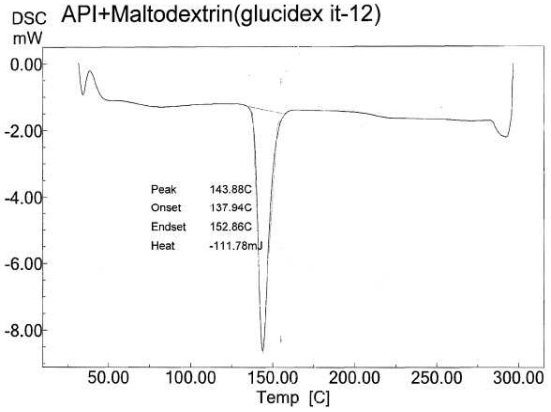
Figure 1
DSC thermograms of Loratadine with major excipients.

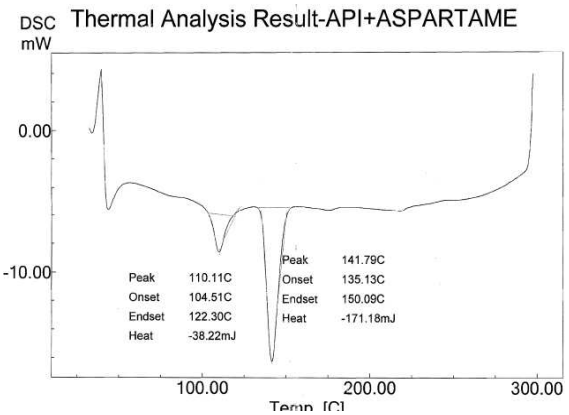


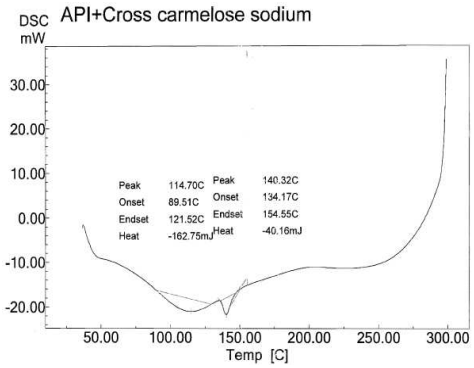


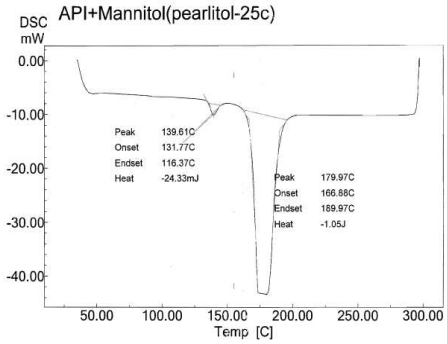












Evaluation of tablets [15]

Friability test:

Friability of tablets was determined using Friabilator (Electrolab, Mumbai). Forty tablets were subjected to the combined effect of abrasions and shock in a Friabilator at 25 rpm and dropping the tablets at a height of six inches in each revolution. Pre weighed sample of tablets were placed in a Friabilator and subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability is given by the formula:

$$F = \left(1 - \frac{Wo}{W}\right) \times 100$$

Where, W_o is the weight of the tablets before the test and W is the weight of the tablet after the test.

Hardness:

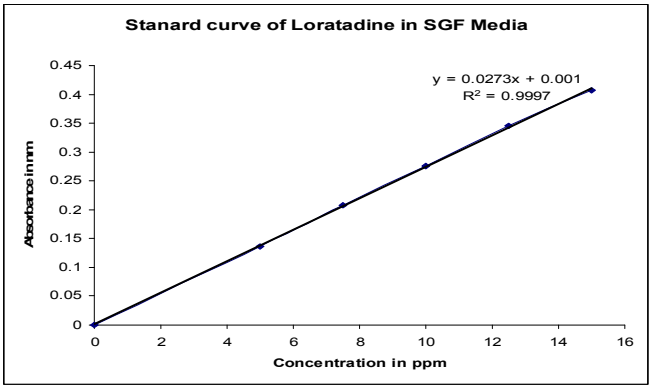
Hardness or tablet crushing strength (F_c) for ten tablets were measured using Dr.Schleuniger digital hardness tester.

Drug content:

Twenty tablets were selected randomly and powdered. A quantity of this powder corresponding to 50 mg of Loratadine was dissolved in 500 ml of simulated gastric fluid (SGF) without enzyme, stirred for 60 min and filtered. 10 ml of the filtrate was diluted to 100 ml with simulated gastric fluid (SGF) without enzyme, Absorbance of this solution was measured using UV spectrophotometer (SHIMADZU 1700) at 278 nm using simulated gastric fluid (SGF) without enzyme as blank and content of Loratadine was estimated.(Fig.2).

Figure 2

Absorbance values for Standard Calibration Curve in Simulated Gastric Fluid (SGF) without enzyme, (λ_{max} 278nm)



Standard calibration curve of Loratadine in SGF media

Measurement of liquid uptake:
A glass Petri dish was partially filled with water and a tablet was placed on the surface of a band of filter paper supported on a glass slide. The uptake of water occurred from the lower surface of the tablet. The time required for water to reach the center of the upper surface of the tablet was noted as wetting time.

Water absorption ratio:
A piece of tissue paper was folded twice and placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio R, was determined using the following equation:

$$R = 100 \times \left(\frac{Wa - Wb}{Wb}\right)$$

Where W_b is weight of the tablet before absorption and W_a is weight of tablet after water absorption.

Disintegration time:
The time required for disintegration of six tablets, placed in each tube of disintegration apparatus USP (Electrolab ED-2L) was measured at 37±2°C using 900ml of distilled water.

Dissolution studies:
The tablet samples were subjected to in-vitro dissolution studies using USP Type-I (Basket) dissolution apparatus (LABINDIA DISSO2000) at 37±2°C and 50 rpm speed. As per the official recommendation of USFDA, 900 ml of simulated gastric fluid without enzyme was used as dissolution medium. Aliquot equal to 10 ml was withdrawn at sampling time of 2, 4, 6, 8, 10 minutes and the dissolution media volume was complimented with fresh and equal volume of blank media. The aliquots were filtered and scanned with appropriate dilution and amount of Loratadine released from the tablet samples was determined spectrophotometrically at a wavelength of 278 nm by comparing with the standard calibration curve and results were obtained as shown in table 4.

Table 3
Evaluation of tablets

Formulation	Friability (%)	Hardness$^{\alpha}$ ±S.D(N)	Weight$^{\alpha}$ ± S.D (mg)	Disintegration time (sec)	Water absorption ratio (%)	Wetting time $^{\beta}$ (sec)	Drug content (%)
Trial 001	0.28	54.7±3.26	170.44±1.03	20-21	33.80	42	99.84
Trial 002	0.29	58.3±3.59	170.36±0.71	25-30	34.02	48	99.67
Trial 003	0.25	59.2±3.59	170.7±0.88	15-20	43.98	35	100.29
Trial 004	0.32	52.5±2.99	170.49±1.11	15-20	47.36	35	100.62
Trial 005	0.18	61.6±4.19	170.9±1.16	135-150	46.36	100	98.24
Trial 006	0.2	61.4±4.19	170.72±0.76	25-30	48.75	38	99.96
Trial 007	0.20	57.8±5.21	170.66±0.92	25-30	48.87	34	101.84
Trial 008	0.27	61.5±3.05	170.72±0.79	15-20	51.08	32	100.5
Trial 009	0.13	52.6±2.83	170.05±0.25	30-35	50.9	32	99.98

α = Average of ten determinations
β= Average of three determinations

Table 4
Percentage of cumulative drug release of all formulations

Time (min)	% Cumulative Drug Release								
	Trial 001	Trial 002	Trial 003	Trial 004	Trial 005	Trial 006	Trial 007	Trial 008	Trial 009
0	0	0	0	0	0	0	0	0	0
2	73	73	77	79	68	72	70	78	79
4	77	78	86	87	76	78	77	87	87
6	85	85	92	93	82	85	83	93	95
8	90	90	93	95	92	94	92	95	98
10	94	93	97	98	94	96	96	98	99

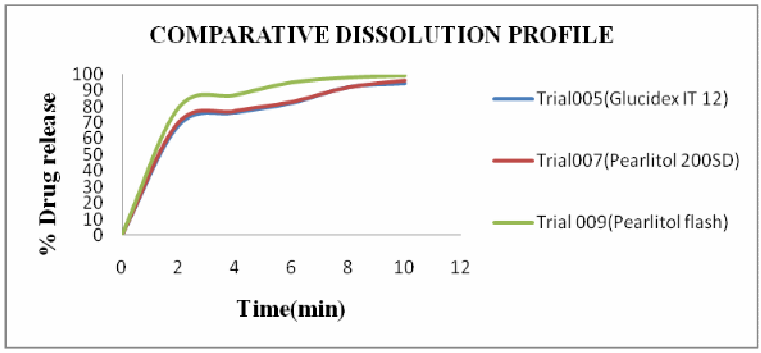


Figure 3
Comparative dissolution profiles of three different diluents used in formulation.

RESULTS AND DISCUSSION

The growing importance of orally dispersible tablets was under lined recently when European Pharmacopoeia adopted the term "Orodispersible tablets" and given the limit as 3 min for dispersion in the mouth, when taken orally.

These above formulations being prepared by direct compression method is versatile and simple and very easy to process. The results are very promising with respect to release profiles and disintegration time within limits.
The formulation of orally disintegrating tablets mainly depends on the type of super disintegrants used like Croscarmellose Sodium (Ac-Di-Sol SD-711) and PEARLITOL flash, a combination of Mannitol and Starch used as direct compressible diluent along with Sodium bicarbonate and Citric acid showed good results with 99.98% drug content, 35 Seconds disintegration time, 0.13% friability and 99 % drug release in 10 minutes (Table 4) along with very good mouth feel.

The absorption maximum (λ_{max}) for Loratadine was found to be 278 nm in simulated gastric fluid. Standard calibration curve (fig 2) of Loratadine was measured in simulated gastric fluid and was found to be linear with correlation coefficient being 0.9997. Wherever possible, mean of the readings were taken to minimize the errors.

Good hardness was achieved in almost all the formulations. In trial 005 where the increased disintegration time and the wetting time (table 3) was observed with increased quantity of Maltodextrin as shown in (table 1).

The compressed tablets showed less weight variation with standard deviation of 1.16 in trial 005 being the maximum amongst all the trials. Weight variation was found to be least in trial 009.

The drug and the excipients subjected to accelerated stress conditions showed promising results as there was no significant change in the DSC chromatograms of the drug indicating the absence of incompatibility of the drug with the excipients with regard to the excipients present in the formulation and the ratio of drug to excipients designed.

All the above nine formulations were prepared and evaluated. Table 1 showed that all formulated tablets exhibited low weight variation and less friability. The prepared tablets showed good drug content. The dissolution data reveals that drug release was within acceptable limits. Incorporation of Maltodextrin (Glucidex IT 12) instead of mannitol (Pearlitol 200SD) increased the disintegration time and wetting time. The *in vitro* dissolution profiles of trial 005, trial 007 and trial 009 comparing the best release profiles amongst the three excipients like Maltodextrin (Glucidex IT 12), mannitol (Pearlitol 200SD) and Pearlitol flash respectively as shown (fig 3).

The incorporation of Pearlitol flash, sodium bicarbonate along with citric acid showed very fast disintegration with less friability and good hardness. The wetting time was least with the formulation having Pearlitol flash and mannitol. Incorporation of maltodextrin as diluent resulted in reduced drug content along with increased wetting time and disintegration time.

CONCLUSION

The above results suggest that the formulated orally disintegrating tablets of Loratadine exhibited good physical parameters and rapidly disintegrating without affecting the release profile and is very effective in case of elderly and pediatric patients. The overall results indicated that trial 009 had a higher edge compared to other trials satisfying all the criteria for a orally disintegrating tablet.
This direct compression process is simple, reproducible and robust to prepare orally disintegrating tablets of Loratadine and other antihistamine drugs using Mannitol, a combination of Mannitol and Starch (Pearlitol flash), Micro crystalline cellulose (Avicel-pH102) and super disintegrants like Croscarmellose Sodium (Ac-Di-Sol SD-711).

REFERENCES

1. Bi Y, Preparation and evaluation of compressed tablet rapidly disintegrating in the oral cavity, Chem. Pharm.Bull., 44(11):2121-2127,(1996).
2. European pharmacopoeia, 6th edition,vol.1, pg750, (2008)
3. 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).
4. Ito A, Sugihara M, Development of oral dosage form for elderly patients: Use of agar as base of rapidly disintegrating oral tablets, Chem.Pharm.Bull, 44(11):2132-2136, (1996).
5. Wehling F, Shuehle S, Madamala N, Effervescent dosage form with microparticles.
   US Patent No. 5,178,878, 1993.
6. Shirwaikar AA, Fast Disintegrating tablets of Atenolol by Dry Granulation Method. Ind.J.Pharm.Sci. 66(4): 422-426,(2004).
7. Fuisz RC. Rapidly dissoluble medicinal dosage unit and method of manufacture, US Patent No 4,855,326, 1989

8. Cherkuri SR, Process for forming quickly dispersing comestible unit and product there from, U.S. Patent No 5,587,172, 1996.
9. Myers GL, Battist GE, Fuisz RC. Process and apparatus for making rapidly dissolving dosage units and product therefrom, U.S. Patent No 5,622,719, 1997.
10. Myers GL, Battist GE, Fuisz RC. Process and apparatus for making rapidly dissolving dosage units and product there from, U.S. Patent No 5,866,163, 1999.
11. Misra TK, Currington JW, Kamath SA, Sanghvi PP, Sisak JR, Raiden MG. Fast dissolving comestible units formed under high speed/ high pressure conditions. U.S Patent No 5,869,098, 1999.
12. Mizumito T, Masuda Y, Kukui M. intrabuccally dissolving compressed moldings and production process thereof. U.S. Patent No 5,576,014, 1996.
13. Joshi AA, Xavier D. Added functionality excipients. Pharm.Technol. (Excipients and solid dosage forms),12-19,(2004)
14. Borsadia S, O'Halloran D, Osborne JL: Quick dissolving films.-A Novel Approach to Drug Delivery, Drug Delivery Technology 2003;3(3):63-66.
15. Gandhi PP, Vaidya KA, Shelake GT *et al.* "Formulation and evaluation of Metformin hydrochloride fast disintegrating tablets by using polacrilin potassium NF from different sources as superdisintegrants". Int.J.Pharmacy Pharm Sci .Vol 2 suppl.2. (2010).

ISSN 0975-6299 Vol 2/Issue 2/Apr-Jun 2011