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Formulation development and optimization of multiple unit particles system (MUPS) containing Ramipril and Hydrochlorothiazide

Hiren P. Patel*[2], Jayvadan K. Patel[1], Ravikumar R. Patel[1] and Manish P. Patel[1]

Nootan Pharmacy College, S. P. Sahkar Vidhyadham, Visnagar, Mehsana, Gujarat, India
Torrent Research Center, Gandhinagar, Gujarat, India

Abstract

Conventional immediate release drug delivery system are based on single or multiple-unit reservoir or matrix system, which are designed to provide immediate drug levels in short period of time. Immediate release drug delivery is desirable for drugs having long biological half life, high bioavailability, lower clearance and lower elimination half life. But main criterion for immediate release dosage form is poor solubility of the drug and need the immediate action of drug to treat any unwanted defect or disease. The present invention relates to produce Multiple Unit Particle System (MUPS) of stabilized Ramipril pellets, Hydrochlorothiazide, diluents, superdisintegrants and lubricants which produce better dissolution of the System for better bioavailability with improving stability and bioavailability of Ramipril. More particularly, the present invention is directed for stabilized Ramipril against decomposition into degradation products, namely, Ramipril-DKP and Ramipril-diacid, during formulation and storage conditions. Simple Ramipril formulation shows 15.15 % Related impurities after 3 month accelerated stability study which was minimized to the 2.07% related impurities in Ramipril pellets after 6 month accelerated stability study. By making MUPS of Ramipril pellets, Hydrochlorothiazide and other excipients shows better dissolution (100.4 % of Ramipril and 97.9 % of Hydrochlorothiazide within 60 minutes) to produce better bioavailability. So, by making MUPS containing Ramipril pellets with polymer coating and Hydrochlorothiazide and other excipients shown better stability of Ramipril along degradation and synergistic effect amongst hypertension in immediate delivery.

Key words: Multiple Unit Particle System, bioavailability, Hydrochlorothiazide, Ramipril pellets, polymer coating.

INTRODUCTION

Hypertension, commonly referred to as “high blood pressure”, is a medical condition where the pressure is chronically elevated is one of the commonly found diseases, affecting most of the populations in the world. So, for treating hypertension effectively is main criterion of study. For treating hypertension, commonly used drugs include ACE inhibitors, Alpha Blockers, Beta Blockers, Calcium Channel Blocker, Diuretics and combination of any of these categories in immediate action required.

Conventional immediate release drug delivery system are based on single or multiple-unit reservoir or matrix system, which are designed to provide immediate drug levels in short period of time. Immediate release drug delivery is desirable for drugs having long biological half life, high bioavailability, lower clearance and lower elimination half life. But main criterion for immediate release dosage form is poor solubility of the drug and need the immediate action of drug to treat any unwanted defect or disease.

Ramipril is a prodrug and is converted to the active metabolite Ramiprilat by liver esterase enzymes, is an angiotensin-converting enzyme (ACE) inhibitor, used to treat hypertension and congestive heart failure. Its long biological Half life (3-16 hours) and its dose (2.5 mg / day) and long elimination phase (9-18 hours) suggest the its immediate action for treating hypertension[1]. studied combination of Ramipril with other diuretic provides synergistic antihypertensive effect in controlling blood pressure in hypertension along with a significant regression of left ventricular hypertrophy. Also, hypertensive patients not much responding to monotherapy with Ramipril, showed significant reduction in blood pressure when shifted to Ramipril-diuretic combination. Among all diuretics, Hydrochlorothiazide has the low dosage, poor solubility, and long half life to treat hypertension. So, combination of Ramipril and Hydrochlorothiazide provide synergistic effects in the treatment of mild to moderate hypertension[2**].** So**,** this study focused on the development of immediate drug delivery of Ramipril and Hydrochlorothiazide**.**

As Ramipril needs special care when formulating into pharmaceutical preparations due the physical stress associated with formulating processes which can increase the rate the decomposition of ramipril into degradant products. Indeed, factors that influence the stability of ramipril formulations are mechanical stress, compression, manufacturing processes, excipients, storage conditions, heat and moisture[3,4,5]**.** So, special formulation for ramipril is required is, Pellets, which gives more stability to Ramipril from compression and other stress condition during formulation and storage conditions. And also Pellets offers some additional advantages like, disperse freely in GI tract, maximize drug absorption, and minimize local irritation of the drug which indicates pellets can be used for immediate drug delivery[6,7].

With regard to the final dosage form, the multiparticulates can be filled into hard gelatin capsules or be compressed into tablets. The compression of multiparticulates into tablets is becoming more popular, especially in the USA, where hard gelatin capsules have been tampered [8,9,10]. So, this study focused on the development of immediate release tablets containing pellets.

MATERIALS AND METHODS

Materials

Ramipril (Hetero labs), Hydrochlorothiazide (Unichem labs), Microcrystalline cellulose (FMC Biopolymer), Mannitol (Roquette, Signet chem. Corp), Starch (Roquette), Crosscarmellose sodium (FMC Biopolymer), hydroxy propyl methyl cellulose (Shinetsu), Talc (Ferro-Belgium), Magnesium Stearate (Ferro-Belgium), Colloidal silicone dioxide (Degussa).

Preliminary trials

Preliminary study trials were carried out for formulation of Ramipril /HCTZ tablets. Literature survey show that ramipril is very sensitive to light moisture, physical or chemical stress and in contact with this Ramipril is degrade in to the ramipril- diketopiperazine by cyclization or condensation[11,12,13]. This is tested by doing these preliminary trials for tablet formulation. For the stability improvement and better formulation of ramipril and hydrochlorothiazide, preliminary trials by direct compression method and wet granulation method were tried and compacted in to tablets. And bilayer technology of both individual drugs was also tried for better formulation by compaction method.

Preparation of ramipril pellets by fluidized bed processing method

Trial & error method was used for the development of formulation of ramipril pellets. With reservoir type coated pellet dosage forms, the polymeric coating must be able to withstand the compression force; it can deform, but should not rupture. Without sufficient elasticity of the film, the coating could rupture during compression and the extended release properties would be lost. In addition, the bead core should also have some degree of plasticity, which can accommodate changes in shape and deformation during Tableting[14]. So, MCC can be used for the core material for drug coating. But directly drug coating on MCC will create compatibility problem or stress to the ramipril, so, film coating on MCC will overcome this problem and also give the elasticity to the drug. Film coated ramipril pellets were prepared by seal coating with hydroxy propyl methyl cellulose and then drug coating on same pellets and finally film coating was performed on drug coated pellets.

Seal coating on base materials

Polymer used for seal coating was hydroxy propyl methyl cellulose which is used as film former in 5 – 15% concentration. So, trial starting with the 5% concentration of polymer for seal coating. And glidant was used in min concentration and seal coating was done on MCC as a core material[15]. Seal coating on MCC was done by Fluid bed processor (GLATT machine) using solution of hydroxy propyl methyl cellulose in water with talc as a glidant.

Drug coating on seal coated pellets

Drug coating was performed on seal coated pellets along with Binder hydroxy propyl methyl cellulose. Polymer concentration had been taken from 2% to 6% because hydroxy propyl methyl cellulose has been used as binder in this range of concentration. Here binder was used because of drug particles can stick to the seal coated pellets and make a uniform drug coating on seal coated pellets and appropriate amount of drug to be contained in to selected quantity of pellets. Drug coating on seal coated pellets was done by solution of Ramipril in solvent with binder in fluid bed processor.

Film coating on drug coated pellets

Film coating on drug coated pellets was varied by different concentration of hydroxy propyl methyl cellulose polymer used as a film former. For film coating polymer concentration taken in to range of 5 – 15%. Theoretically amount of polymer required for film coating is higher than seal coating. So, for film coating polymer concentration taken was in range of 5% to 15%. Talc was added for reducing the static charge in to pellets. By adding talc in to spraying solution, evaporate during spraying and stick to the pellets and remove the static charge of pellets during spraying and drying[16].

Tableting of coated pellets with hydrochlorothiazide and other excipients

Ramipril / Hydrochlorothiazide Tablets were done by using different concentration of and different proportion of Diluents. Disintegrating agent like Sodium Starch Glycolate (SSG), was used as disintegrating agents in different concentration in tablet formulation. The usual concentration of SSG employed in a formulation is between 2% and 8%[17,18], with the optimum concentration about 4%, although in many cases 2% is sufficient[19,20,21]. All disintegrating agent are water insoluble. Disintegrants is added to formulations to facilitate breakup of the tablet when in contact with water in the GIT. They may function by drawing water in to the tablet and swelling causing it to burst apart[22,23].

Diluents like MCC and Mannitol were used for formulation development. Because, Tableting of pellets with diluents produce breakage or rupture of pellets and that will affect on dissolution profile and stability of tablet. This problem is solved by the using of different granular MCC grade which are available with greater plasticity[24,25]. So, granular grade of MCC and Mannitol were used for trial of tablets.

Evaluation properties of pellets[26,27,28]

Particle size distribution study of pellets was performed by sieving analysis using a nest of standard sieves and the desirable range of pellets was taken to be between 450 - 1180 mm. The post-compaction tests of pellets were performed they included assay, in vitro dissolution study in 0.1 N HCl at specified time interval and measure the concentration release in time profile by HPLC. Ramipril pellets were subjected to the Accelerated Stability studies in Aluminum / Aluminum pouch. As the dosage form is formulated for delivery to stomach, no change should occur in its %dissolution profile and related impurities. Ramipril is very sensitive to light, moisture and any physical or chemical stress, For study tablets prepared from pellets and only pellets were packed in aluminum pouch and in vial respectively, charged for accelerated stability study at 40^0 C and 75% RH for 3 months in a chamber. Stability study of pellets were performed by, first checking the initial parameters of pellets Then put it in specified condition for 1 month. After 1 month check for all parameters. If it shows satisfactory results then continue the test for next month and continue for 3 months.

Evaluation properties of tablets

The post-compaction tests were performed on the tablets at least 24 h following preparation and they included the determination of weight, thickness, drug content uniformity, friability (Erweka friabilator, Germany), hardness (tablet hardness tester, Schleuniger Pharmaton 6D Model, USA), disintegration (Erweka ZT 44, Germany) and dissolution testing in 0.1 N HCl, for formulations

containing coated pellets[29,30,31]. All tests were performed on at least five replicates. The degree of damage to drug pellets was assessed by the use of the *similarity factor…*

$$F_2 = 50 * log \{[1 + (1/n) \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} * 100\}$$

Where *Rt* and *Tt* are the per cent dissolved at each time point for reference (*R*) and test (*T)* products. An *f*2 value between 50± 100 suggests that the two dissolution profiles are similar and the mean dissolution profiles are assumed to differ by no more than 15%at any time point[32]. An accelerated Stability study was also performed in Aluminum / Aluminum pouch of the tablets.

RESULTS AND DISCUSSION

Preliminary trials

Literature survey show that ramipril is very sensitive to light moisture, physical or chemical stress and in contact with this Ramipril is degrade in to the ramipril- diketopiperazine by cyclization or condensation. This is tested by doing these preliminary trials for tablet formulation. In the direct compression flow of the blend and parameters of tablets were major problem. Where in wet granulation method parameters are in range but as the properties of ramipril, it is degrade and showing stability problem. Same problem also can obtain in bilayer formulation because it was also prepared by stress. And also the tablet parameters were not getting in the range.

Table 1. Accelerated stability study data of tablets prepared by wet granulation method

Parameters	40^0C 75%RH 1 M	30^0C 75%RH 1 M
% Assay (Ramipril: HCTZ)	93.3 / 95.5	99.3 / 96.2
% related impurities (Total impurity)	10.2	6.82
% Dissolution (Ramipril: HCTZ)	90.3 / 90.3	95.1 / 90.4

Seal coating on microcrystalline cellulose

By using granular grade of MCC, pellets were in spherical shape, and properly form. From the comparisons of sieving analysis of different concentration shown that in 7% polymer film coating, pellets are formed and it is very regularly distributed in 60# sieves than other two concentrations. Pellets of this batch were not breaking easily which, show good film formation than other two batches.

Table 2 sieve analysis results of different % concentrations of polymer

ASTM Sieve no.	**% weight retained of Pellets**		
	5% Polymer	**7% Polymer**	**9% Polymer**
# 20	0	0	0
# 40	0.32	12.2	21.6
# 60	53.6	74.9	72.1
# 80	23.7	6.3	4.1
# 100	15.2	2.4	0.9
Below # 100	7.18	4.2	1.3

In 5% film coating, fines of powder seen very high than other two batches and also shown the small quantity of pellets formation than other two batches and also the pellets were break freely means film coating was not properly done. In 9% film coating aggregation of pellets was seen and pellets were stick each other and somewhat slugging observed. So, for next experiment of drug coating on polymer coated pellets will be done with 7% polymer seal coated pellets. Sieve analysis data of different batches shown in table 2.

Drug coating on seal coated pellets

Drug coating on the seal coated pellets with different proportion of binder concentration was evaluated. Three different concentration of binder 2%, 4%, 6% were taken for drug coating. But by appearance of all three batch pellets, 4% binder concentration pellets were seen uniform in shape and size. Sieve analysis study of all three batches shown that drug coated pellets was retained highest on 40# sieve 4% binder concentration than other two concentrations. And also fines were very less observed in 4% binder concentration than 2% binder concentration. Aggregation of pellets was also less in 4% binder concentration than 2% binder concentration. Assay of three different batches was found distributed because of different proportion of binder concentration in different batches. 2% binder concentration assay was observed less and in 6% binder concentration higher than required. But in 4% binder concentration Assay was nearer to required assay. From the P.S.D data and % Assay data, it was concluded that 4% polymer used as a binder shows good drug entrapment and particle size of pellets.

Table 3 Sieve analysis and Assay results of different % concentrations of Binder

ASTM Sieve no.	% weight retained of Pellets		
	2% Binder	4% Binder	6% Binder
# 20	0	0	0.86
# 30	0.2	2.3	8.94
# 40	41.7	73.8	71.9
# 60	32.2	20.4	14.2
# 80	15.4	1	2.1
# 100	3.8	0.7	0.8
Below # 100	6.7	1.8	1.2
% Assay	94.1	99.6	106.8

Film coating on drug coated pellets

From the Sieve analysis study of pellets, batch no. P 18 (8%), P 19 (8.5%) shown good pellets. In 7 and 7.5% concentration polymer film coating on pellets was observed not proper and also plasticity wasn't observed in pellets. Most of the film coated pellets have to retain on the # 30 and # 40 sieve with minimum fines. This criterion was only observed in B. No. P 18 (8%), P 19 (8.5%), P 20 (9.0%). But in Batch P 20 aggregation of pellets was observed in little amount and sticking of pellets occurred to the each other. So from appearance and Sieve analysis study, it was concluded that B. No. P 18 (8%), P 19 (8.5%) show good pellets in comparisons with other batches. % Assay of all batches was acceptable and came in to the range, except batch P 16. % assay results of all batches shown that all batch contain equivalent amount of ramipril within range. Because of final formulation of pellets was tablet, dissolution of pellets was carried out by converting it in to tablet dosage form. In-vitro dissolution data of tablet was compared with the release profile of innovator dosage form (marketed). From the dissolution data, B. No. P 16 (7%)

and P 17 (7.5%) show very fast release of ramipril. This may be because of rupture of pellets during compression and this rupture of pellets also may cause the stability problem of ramipril. While, B. No. P 18 (8%) and P 19 (8.5%) show good and comparable results with the innovator dosage form. And B. No. P 20 (9.0%) show little retardation of release than reference product. So, Batch P 19 (8.5%) show good release and had greater f_2 value than other than other batches.
Stability study of 8.5% polymer concentration film coated pellets shown no degradation of Ramipril and similar dissolution as initial at 40^0 C and 75% RH condition after 3 month. So, formulation of b. no P 19, film coated pellets were taken for next optimization of tablet dosage form.

Table 4. Sieve analysis and Assay and f_2 value results of different % concentrations of film formers

ASTM Sieve no.	**% weight retained of Pellets**				
B. No.	**P 16 (7% polymer)**	**P 17 (7.5% polymer)**	**P 18 (8% polymer)**	**P 19 (8.5% polymer)**	**P 20 (9% polymer)**
# 20	0.7	0.6	1.8	5.8	10.1
# 30	42.8	50.8	55.1	66.1	71.8
# 40	35.8	30.1	30.7	24.3	15.8
# 60	12.2	7.6	4.8	1.3	1.4
# 80	2.5	4.1	4.1	0.7	0.2
# 100	3.3	3.8	2.2	1.1	0
Below # 100	2.7	3	1.3	0.7	0.7
% Assay	**105.1**	**103.3**	**101.8**	**99.8**	**98.0**
F_2 value for dissolution	61.40	66.49	76.62	81.36	60.09

Table 5 accelerated stability study data of different % concentrations of film formers

Parameters	Initial	40^0C 75%RH 3 M
% Assay (Ramipril)	99.8	93.4
% related impurities (Total impurity)	BLOQ	3.63
% Dissolution (Ramipril)	99.8	97.1

Tableting of coated pellets
These studies were performed to optimize the concentration or amount of diluents used MCC (Avicel) and Mannitol (Pearlitol SD 200) to giving the plasticity to pellets and to prevent the rupturing of pellets. In B.No. T1 Only the MCC (Avicel) was used as a diluents (MCC - 100%) and in B. No. T2 both diluents were used in equal amount (MCC – Mannitol: 50% - 50%). And in B. NO. T3 only Mannitol (Pearlitol SD 200 - 100%) was used as a diluents in tablet formulation. All the characteristics of these batches were discussed following.

Results of Micromeritic properties of blend with different ratio of diluents
The Micromeritic properties of different Batches i.e. bulk density, tapped density, compressibility index, Hausner ratio and angle of repose revealed no significant difference among the batches. In B. No. T1 shows the good flow, compressibility and other parameters than other two batches. Loss on drying was also observed to be in the range of 2 to 3% wt/wt for all batches which passes the USP requirements. Thus, form the Micromeritic data it is evident that

blends of different batches possess comparable compressibility and flow properties of all batches prepared with MCC and Pearlitol SD 200.

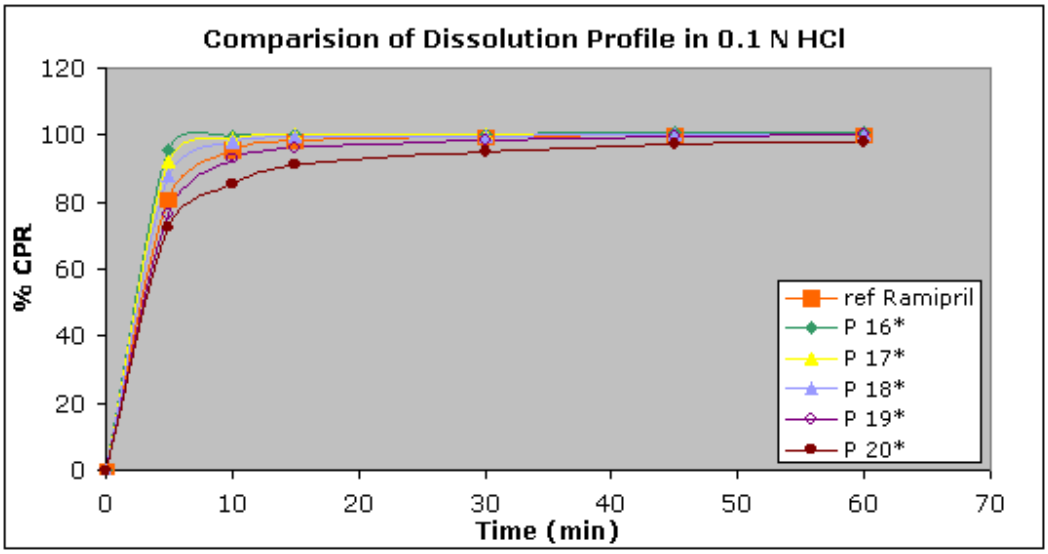

Figure 1 Dissolution profiling of different % concentrations of film formers

Table 6 Micromeritic properties of blend with different ratio of diluents (B. T1, T2, T3)

Batch code	B.D (gm/cc)	T.D (gm/cc)	C.I (%)	H.R	A.R (ϕ)	% LOD
T 1 (100% -MCC)	0.64	0.72	12.82	1.15	26.50	2.45
T 2 (50/50% - MCC/ Mannitol)	0.63	0.73	13.79	1.16	24.10	2.61
T 3 (100% - Mannitol)	0.61	0.75	18.66	1.23	31.45	2.09

Physical characteristics of tablets

The tablets of different batches were prepared at same adjustment of machine, after that physical characteristic were found to be consistent as in all batches and shown in table 6.2.3. All characteristic of tablets were within limit and acceptable and comparable with the reference product except the disintegration time and friability.

Table 7 Physical characteristics of tablet with different ratio of diluents (B. T1, T2, T3)

Batch code	Avg. Weight (mg)	Hardness (N)	Thickness (mm)	Friability (% w/w)	D.T. (min)
T1(100%-MCC)	196.7 – 201.8	64 - 77	2.92 – 3.07	0.314 %	0.23
T2(50/50%-MCC/ Mannitol)	197.8 – 202.1	51 – 60	3.01 – 3.19	0.395 %	1.26
T3(100%-Mannitol)	197.1 – 200.9	53 – 60	2.98 – 3.13	Capping	4.48

***In vitro* dissolution study**

Tablets containing only MCC showed the very fast dissolution of drug in to dissolution medium. Those results were acceptable and also comparable with reference product. Batch T2 shown the comparable and expected dissolution of tablet. But Batch T3 showed delayed release of tablets

than reference product release. In batch T1 fast release observed because of the only MCC because MCC also used as a Disintegrating agent and as increase the concentration of MCC, it will increase disintegration of tablets. In Batch T3 only Pearlitol SD 200 was used which is crystalline, water soluble diluents and do not have any disintegration property. So, this batch showed delayed release due to long time for disintegration of tablets. But in Batch T2, MCC and Pearlitol SD 200 were used in same concentration showed similar results to the reference product release. Similarity study of all batches shown in Table, which show that B. No. T3 have F_2 value less than 50 (43.4 % for ramipril and 41.1 % for HCTZ) for both ramipril and HCTZ release compare with reference product release, so this batch was not acceptable. B. No. T1 shown F_2 value in range of 50 – 100 (69.2%% for ramipril and 63.1 % for HCTZ) for both Ramipril and HCTZ release, compare with reference product release. So, this batch was acceptable. But B. No.T2 had shown F_2 value in range of 50 – 100 and also nearer to 100 (87.0%% for ramipril and 88.1% for HCTZ), which shown good similarity with reference product release of Ramipril and HCTZ than Batch no. T1.

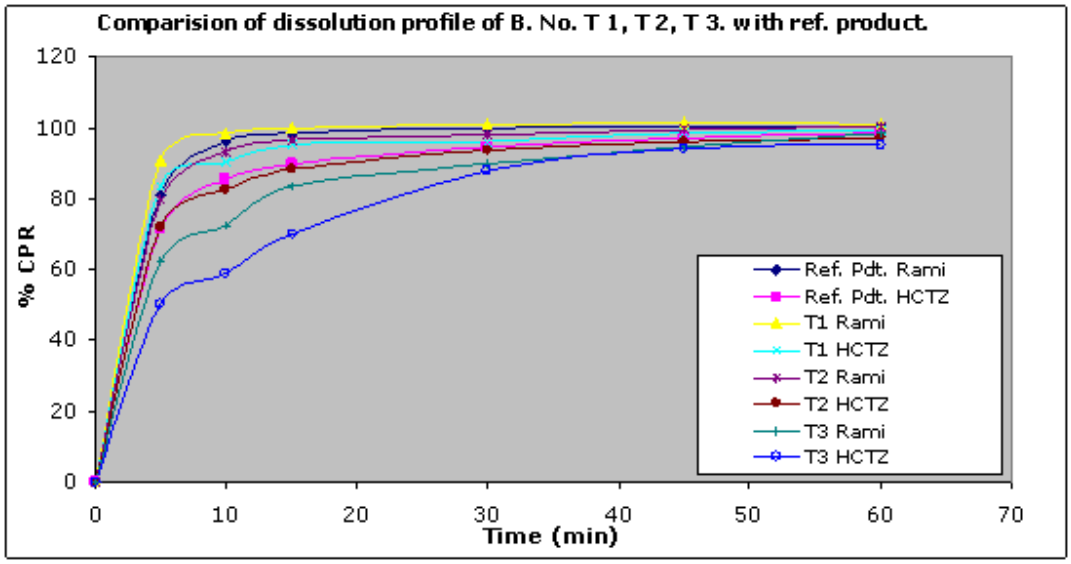

Figure 2 Dissolution profiling of different ratio of diluents (B. T1, T2, T3)

Table 8 F2 Value of tablet with different ratio of diluents (B. T1, T2, T3) with comparison to reference

Batch code	F_2 Value with comparison to reference	
	Ramipril	HCTZ
T 1 (100% -MCC)	**69.2%**	**63.1%**
T 2 (50/50% - MCC/ Mannitol)	**87.0%**	**88.1%**
T 3 (100% - Mannitol)	**43.4%**	**41.1%**

Accelerated stability study

Accelerated stability data shown that ramipril and Hydrochlorothiazide drug were not degraded after 3 months also. And all impurities were also found in acceptable range. After 3 month accelerated stability study there was also not any change occurs in to the tablet disintegration

time and water content of the tablets. After three month dissolution of tablets were performed and compare it with the initial dissolution of tablets. These results were not changed too much during 3 month.

Table 9 accelerated stability study data of different ratio of diluents

Parameters	**Initial**	**40^{0}C 75%RH 3 M**	**30^{0}C 75%RH 3 M**
% Assay (Ramipril: HCTZ)	100.3 / 98.8	97.7 / 97.8	100.2 / 98.3
% related impurities (Total impurity)	BLOQ	2.35	1.49
% Dissolution (Ramipril: HCTZ) in 45 min	99.7 / 96.2	97.6 / 94.7	98.3 / 95.1
%Water Content	3.89	6.63	6.62
Disintegration time (min)	1 - 17	1 – 37	1 - 29

CONCLUSION

Formulation development of Ramipril pellets for stability improving of Ramipril from stress condition with required dissolution of tablets were tried with film coating shown decrease in the degradation of the Ramipril after formulation process. After 3 month accelerated stability study of Ramipril pellets and MUPS have shown related impurities respectively 2.35 % and 1.49% which complied the limit of impurities (NMT 5.0%) required in final formulation.

MUPS prepared with super disintegrating agents showed 100.3 % Dissolution of Ramipril and 98.8 % Dissolution of Hydrochlorothiazide within 45 minutes. Which shown better dissolution of the MUPS was achieved within 45 minutes.

Whole investigation summarized that MUPS prepared with incorporating Ramipril pellets and Hydrochlorothiazide with other excipients shown good stability along degradation of Ramipril and Immediate action of tablet with highest bioavailabity of both drugs.

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