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Research Article

Studies on formulation development and in-vitro release kinetics of Ramipril Micropellets for controlled release

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ABSTRACT
MicroPellets are agglomerates of fine powders or granules of bulk drugs and excipients. They consist of small, free flowing, spherical or semi- spherical solid units, typically from about 0.5mm to 1.5mm, and are intended usually for oral administration. Pellets can be prepared by many methods, the compaction and drug-layering being the most widely used Today. The study was undertaken with an aim to develop controlled release micropellets dosage form for Ramipril which is a anti hypertensive agent and is one of the most widely used drugs for treating mild and hypertension. The approach of the present these polymers and excipients and to assess the effect of physicochemical nature of the active ingredients on the drug release profile. The prototype formulation of micro pellets were prepared using the fluid bed coater (FBC) with the air pressure 2.0 bar and the spray rate 10-15ml/min. Temperature of bed is varied from 35°C to 50°C and inlet temperature is varied from 50°C to 70°C and the effect of various parameter were observed such as air pressure, inlet and outlet temperature of FBC, it is observed that at high pressure the pellets are breaking. For bed and inlet temperature it is observed that at low temperature lumps are occurring in the formulation and at 2.0 bar air pressure,inlet temperature 60°C and bed temperature of 40°C is reliable for solution flow rate 10-15ml/min. Concerning results of prototype preparation of Ramipril the micro pellets were prepared using HPMC Ethyl cellulose polymer as release retardant in six different concentration i.e. EC-14 2%, 4%, Cow ghee, EC-20 2%, 4%, 6%. Formulated micro pellets showed delayed *in vitro* dissolution behavior, probably due to optimized concentration of polymer. The micro pellets drug was stable at room temperature, 25°C/60% RH, 30°C/65% RH and 40°C/75% RH as per ICH guidelines, after 3 months.
Key words: Micropellets, Ramipril, HPMC, Ethyl Cellulose.

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 Ramipril at by liver esterase enzymes, is an angiotensin converting enzyme (ACE) inhibitor, used to treat hypertension and congestive heart failure. Its long biological Half life (3-16hours) and its dose (2.5 mg / day) and long elimination phase (918hours) suggest the it’s immediate action for treating hypertension. 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, recipients, 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.

MATERIAL AND METHODS

Materials

Ramipril (Hetero labs), hydrochlorothiazide (Unichem labs), microcrystalline cellulose (FMC Biopolymer-),mannitol (Roquette, Signet Chem. Corp), starch (Roquette), cross-carmellose sodium (FMC Biopolymer), hydroxy propyl methyl cellulose (Shinetsu), talc (Ferro-Belgium), magnesium stearate (Ferro-Belgium), colloidal silicone dioxide (Degussa).

Description of Manufacturing Process and Process Controls

STAGE I

Table 1. Formula for Stage 1.

Raw materials	Quantity
Ramipril	10gm
PVP K-30	6gm
Mg.Sterate	36mg
Micro-Pellets	55gm

Note: Pass all powdered material through 100 mesh size sieve before adding to get uniform Particle size.

STAGE II

Table 2. Formula for Stage 2

Raw materials	Quantity
Stage I pellets	Total Quantity

Process:

1. Dry the Stage I pellets in SS Tray Drier at 45^0C for 8 hours.
2. Check moisture content. It should be below 1%.
3. Pass the dried Pellets through sifter to remove fines.

STAGE III

Table 3. Formula for Stage 3

Raw materials	Quantity
Stage II dried pellets	Total Quantity
Hydroxy Propyl Methyl Cellulose (HPMC)	1%
Purified Water	100ml.

Process:

1. In clean and dry SS vessel, Charge Purified Water and Hydroxy Propyl Methyl Cellulose 5 cps and stir till dissolution to form clear colloidal subcoating solution.
2. In clean, dry coating pan, charge dried Pellets.
3. Spray above coating solution through Nozzle on Pellets along with continuous flow of warm air in Air gun to dry the coat as soon as it forms for uniform coating. Continue coating till minimum 1% w/w weight gain of coated Pellets is achieved.

STAGE IV

Table 4. Formula for Stage IV

Raw materials	Quantity
Stage III sub coated pellets	Total Quantity
1) EC N-14	2%, 4%, 6%
2) EC N-20	2%, 4%, 6%
3) EC N-14+Cow Ghee	1:1 ratio

Evaluation Methods:

Assay:

Dissolve about 300mg of Ramipril accurately weighed in 25mLof methanol add 25mLof water, and titrate with 0.1Nsodium hydroxide determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each ml of 0.1Nsodium hydroxide is equivalent to 41.65mg of ramipril.

Moisture content:

The moisture content is defined as the ratio of the mass of water by weight (m) and the mass of the dried material by weight (m). The formulations were subjected to moisture content study, by placing the micropellets at 60° C for 10 minutes in an IR moisture balance

For determination of the moisture content in the extrudates three samples of extrudates were collected for each batch during the extrusion process and were dried in a vacuum oven (Heraeus VT 6060 M, Kendro, Hanau, Germany) at 60 °C for 336 h. [16] In addition the moisture content of the raw materials was evaluated under the same conditions. The moisture content was calculated based on the dry mass.

$$\text{Moisture content} = \frac{\text{Titre value} \times \text{Separation fluid}}{\text{Weight}} \times 100$$

FTIR Study

The Ramipril pellets were with all the formulation combinations were subjected to FTIR comparative studies along with potassium bromide was used for FTIR (Fourier Transform Infra Red) studies. The I.R spectra were recorded using I.R spectro photometer (Perkin-Elmer FTIR, Perkin Elmer, USA)

Sieve analysis

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. [17] Pellets of this batch were not breaking easily which, show good film formation than other two batches. 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.

In-vitro Dissolution studies:

The USP rotating – paddle Dissolution Rate apparatus (Veego, Mumbai) was used to study drug release from the micropellets.[18] The dissolution parameters [100mg pellets ; 37± 2°C ; 50 rpm ; 500ml of USP Phosphate buffer (pH 6.8); n=3; coefficient of variation< 0.05] were maintained for all the nine formulations. 2ml of aliquot were withdrawn at specified intervals and after suitable dilution assayed by SHIMADZU UV-VIS Pharm Spec 1700 spectrophotometer at 277.5nm. The data for percent drug release was fitted for zero order and Higuchi matrix equation. The polysaccharide did not interfere with the assay as confirmed from conducting a dissolution study of blank alginate beads. The results obtained in a in-vitro release study were plotted in different model of data treatment as follows,

1. Cumulative % release vs time
2. Cumulative % drug to be release vs time
3. Log cumulative % drug to be release vs time.

RESULTS AND DISCUSSIONS.

Calibration curve:

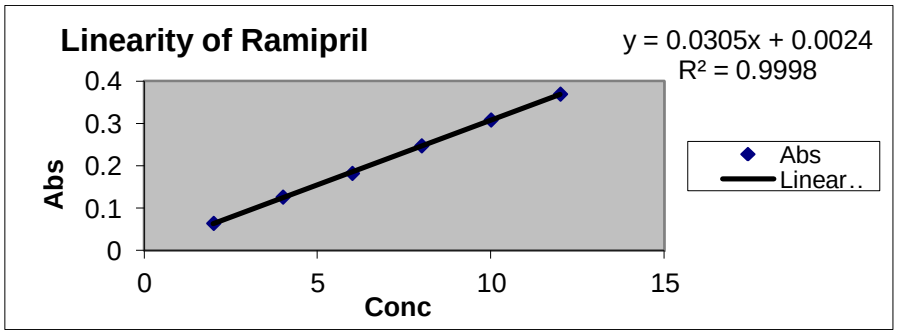

Fig 1: Standard graph for the estimation of Ramipril controlled release micro pellets spectrophotometrically.

Assaay

Assay results of all batches shown that all batches contain equivalent amount of Ramipril within range (as shown in table 1). Because of final formulation of pellets was capsuled, dissolution of pellets was carried out by converting it into capsules.

Table 5 . Assay results of formulation 1 to 7

S.No	Formulation Code	Assay (%)
1	F1	10
2	F2	9.99
3	F3	10.5
4	F4	9.94
5	F5	9.92
6	F6	10.05
7	F7	9.95

Moisture content

Moisture content of different batches was found distributed because of different proportions of polymer concentration in different batch formulations. (as shown in table 1) The polymer concentration which is having less concentration is having less moisture content value and the polymer concentration which is having high concentration is having more moisture content value like F1 and F6.

Table 6. Moisture content results of different % concentrations of Ramipril

S.No	Formulation Code	Mean (%)
1	F1	2.44
2	F2	0.83
3	F3	1.33
4	F4	1.24
5	F5	1.09
6	F6	2.57
7	F7	2.19

F.T.I.R

F.T.I.R of different batches was found distributed because of different proportions of binder concentration in different batches. The I.R studies of different concentrations of Ethyl cellulose E.C N20 (2%), E.C N20 (4%), E.C N20 (6%), E.C N14 (2%), E.C N14 (4%), PVPK, and COWGHEE + RAMIPRIL were studied. To know the impurities and structurally activities of the compounds. It was found to be there was no chemical incompatibility between drug and excipients used in the formulations.

Sieve analysis

From the sieve analysis study of pellets, sieve no: #40 and #60 shown good pellets. [22]In #20 and #30 concentration polymer film coating on pellets was observed not proper and also plasticity was not observed in pellets. Most of the film coated pellets have to retain on the #20 and #30 sieve with minimum fines. So from appearance and sieve analysis study, it was concluded that F2 and F6 show good pellets in comparision with other batches. % assay of all batches was acceptable and came within range. % assay results of all batches show that that all batches shown that all batches contain equivalent amount of Ramipril with in range

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Table 7: Sieve analysis results of different % concentrations of polymers

ASTM Sieve no	% Weight retained of pellets						
	F1	F2	F3	F4	F5	F6	F7
#20	0	0	0.83	0	0	0	0.89
#30	0.3	2.1	8.91	0.2	0.5	2.5	8.92
#40	41.6	73.9	71.7	40.5	41.5	73.6	71.8
#60	32.4	20.5	14.4	33.4	32.5	20.3	14.1
#80	15.2	1.1	2.3	15.6	15.1	1.1	2.2
#100	3.9	0.9	0.6	3.5	3.9	0.9	0.9
Below#100	6.5	1.5	1.2	6.8	6.6	1.7	1.1

In vitro dissolution Sudies

Table 8 : Comparative In vitro dissolution study of Ramipril micropellets from formulation 1 to 7

S.No	Formulation Code	Time in 1hr	2^{nd} hr	3^{rd} hr	4^{th} hr	5^{th} hr
1	F1	41.94	69.14	83.6	85.5	84.76
2	F2	34.7	60.75	82.15	85.33	85.62
3	F3	31.53	57.27	70	85.91	87.65
4	F4	8.67	20.53	29.5	31.82	33.55
5	F5	30.66	54.96	86.78	90.25	90.54
6	F6	23.43	52.36	80.71	86.7	89.4
7	F7	15.91	35.87	58.43	77.81	92.57

Table 9: Comparative pharmacokinetics for formulations F1-F7

Formulation	Zero order kinetics				First order kinetics			
	Slope	r	r2	K-value (hr -1)	Slope	r	r2	K-value (hr -1)
F1	-10.15	-0.86	0.74	10.15	-0.14	-0.9	0.81	0.322
F2	-12.64	-0.9	0.81	12.64	-0.175	-0.94	0.88	0.403
F3	-14.08	-0.96	0.925	14.08	-0.197	-0.98	0.967	0.45
F4	-6.105	-0.93	-0.87	6.105	-0.035	-0.95	0.902	0.08
F5	-15.5	-0.91	0.83	15.5	-0.241	-0.94	0.883	0.55
F6	-16.62	-0.93	0.83	16.62	-0.227	-0.976	0.953	0.522
F7	-19.52	-0.99	-0.995	19.52	-0.25	-0.96	0.93	0.575

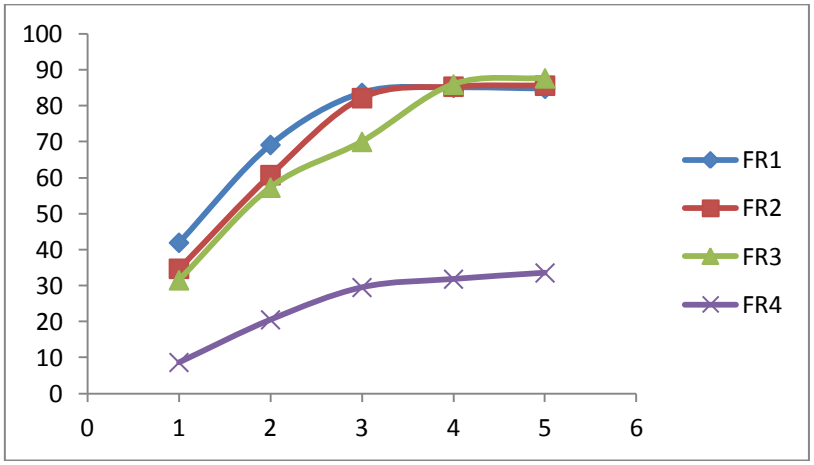

Fig 2:Comparative in vitro drug release profile of ramipril micropellets from formulation 1 to 4

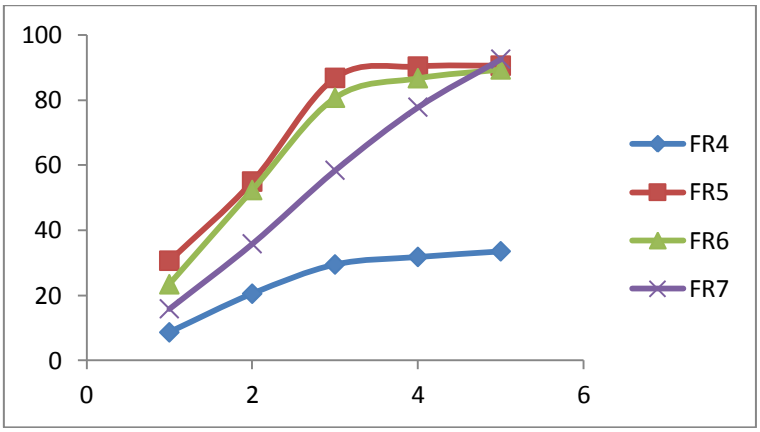

Fig 3:Comparative in vitro drug release profile of ramipril micropellets from formulation 4 to 7

SUMMARY AND CONCLUSION

In the present work, an attempt was made to develop Controlled release Ramipril micro pellets as an improved and better patient compliance dosage form. From the study conducted, the following conclusions are drawn. The F1, F2, F3, F4, F5, F6, F7, formulations were prepared and evaluated. Controlled formulations of Ramipril in the form of controlled micro pellets capsules were developed to a satisfactory level, in terms of drug release (fig: 2 & 3), I.R, assay, moisture content, sieve analysis, invitro dissolution studies. The F1 – F6 formulations follows first order rate kinetics and the F7 formulation follows zero order rate kinetics. The F7 formulation releases the highest amount release of 92.57% at the end of 5th hour.

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