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STABILIZATION OF CALCITRIOL IN TABLET DOSAGE FORM

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ABSTRACT

Calcitriol is calcium channel agonist, antihypocalcaemic, antihypoparathyroid drug used to treat Vitamin D deficiency, refractory rickets, familial hypophosphatemia, hypoparathyroidism and used in the management of hypocalcemia & renal osteodystropy in patients with chronic renal failure undergoing dialysis. It is available in soft gelatin capsules form in market which accounts for its high cost. Calcitriol is heat, light and water sensitive so difficult to formulate in tablet dosage form. So present work is an attempt to stabilize calcitriol in tablet dosage form and formulate a calcitriol tablet of portable price. In the present work tablets of model drug was prepared by using medium chain triglycerides & combination of antioxidants. Starch was used to provide good powder flow. Forced degradation study was done to get know how of various degradation pathways of API & we found that oxidation is major degradative pathway of calcitriol. Drug-excipients compatibility studies are done at 40 ºC/75 %RH and 60 ºC & it is observed that no common excipients are creating any drastic change in the mixture with model drug. Stability studies for 1 month on final formulation were analysed for percent drug release, friability, thickness, hardness and drug content. No appreciable difference was observed in physical parameters as well as in % drug release.

INTRODUCTION

Drug may be administered by variety of routes but oral administration is adopted wherever possible. It is the safest, easiest, and most economical route of drug administration[1]. Calcitriol is chemically (5Z, 7E)-9, 10-Secocholesta-5, 7, 10(19)-triene-1a, 3b, 25-triol, having chemical formula $C_{27}H_{44}O_3$ [2]. It is used to treat Vitamin D deficiency, refractory rickets, familial hypophosphatemia and hypoparathyroidism, and in the management of hypocalcemia & renal osteodystropy in patients with chronic renal failure undergoing dialysis. Also used in conjunction with calcium in the management and prevention of primary or corticosteroid-induced osteoporosis [3].

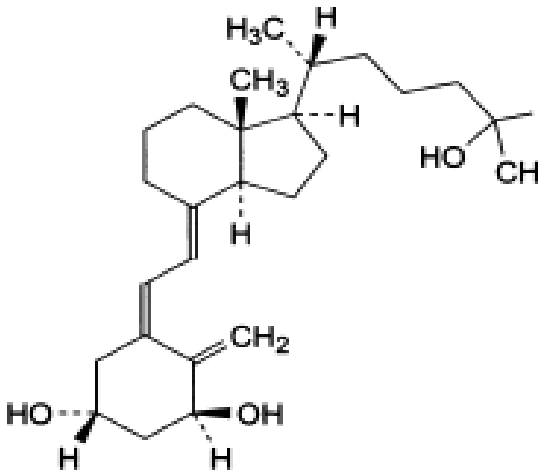


Figure1 Chemical structure of Calcitriol [4]

MECHANISM OF ACTION [2, 3]

Calcitriol, a pharmaceutical form of vitamin D, has anti-osteoporotic, Immunomodulatry, Anticarcinogenic, antipsoriatic, antioxidant, & mood modulatory activities.

- Antiproliferative activity for keratinocytes & stimulation of epidermal cell differentiation- anti-psoriasis activity.
- Anticarcinogenic activity -Vitamin D receptors (VDRs) interact with retenoic acid X receptors & form Vitamin D responsive elements which activate or repress transcription of target genes.
- Immunomodulatry activity- mediated by VDRs which are expressed in monocytes but induced upon activation of T & B lymphocytes.
- Calcium channel agonist.

Meignant et al mentions the use of at least one dry and moist binder combined in synergistic quantity with at least one diluents, at least one binder, at least one lubricant, at least one of said diluents and said binder being a sweetening agent [5].

Andon et al studied combined effect of calcium and vitamin D formulation. These supplements are useful for increasing bone growth & for treating age related bone loss in humans and animals. Estrogen is also used as supplement since it affects metabolism of calcium by influencing osteoblast cells [6].

Shojaei et al mentions the use of capsule stabilizing agent selected from mono-di-triglycerides, mono-di-fatty esters of polyethylene glycol, fatty acids and combinations i.e. oral capsule formulation with increased physical stability [7]. Flashner Barak et al mentions large number of possible delivery methods (oral, nasal, sublingual, vaginal, rectal, intravenous, intramuscular, intra-arterial or topical) for administration of an active vitamin D for treating liver disease [8]. Burnside et al mentions solid dosage forms containing liquid ingredients e.g.-liquid active agents, liquid oral absorption enhancer or liquid solvents for selected drugs and process to prepare those [9]. Pasi Merkku et aldescribe the influence of three independent fluidized bed granulation process variables (inlet air temperature, atomozing air pressure and binder solution amount) on flow rate of granules and tablet properties. The flow time of the granules was affected by all these three factors. But the influence of inlet air temperature on the responses was insignificant [10].

MATERIAL AND METHODS

MATERIALS

TABLE 1: LIST OF MATERIALS

S.No	Name of material	Use	Source
1	Calcitriol	API	Biocon
2	Cross carmallose sodium	Disintegrant	Cadilla Pharma
3	Microcrystalline cellulose powder	Diluent	Sigachi chloro chemicals
4	Poly vinyl pyrolidine	Binder	Zhejiang al pharma.
5	MCC RQ 102	Diluent	Cadilla Pharma
6	Sodium starch glycolate	Disintegrant	Cadilla Pharma
7	Butylated hydroxy anisole	Antioxidant	Finar chemicals

8	Butylated hydroxy toulene	Antioxidant	Finar chemicals
9	Soyabean oil	Vehicle	Sema international
10	Hydroxy propyl methyl cellulose	Seal coat	Cadilla Pharma
11	Magnesium sterate	Lubricant	Cadilla Pharma
12	Talc	Glidant	Cadilla Pharma
13	Starch	Binder	Cadilla Pharma
14	Polyethylene glycol	Plasticizer	Cadilla Pharma
15	Instamoist shield	Coating agent	Ideal Cures
16	Calcium Carbonate	API	Paragon industries

METHOD

Formulations F_{1-5} gives us idea about feasibility of excipients in tablet dosage form. Next trials were taken with calcitriol.

Table 2: Formulation of tablets of Model drug (For 1 tablet = 1500 mg)

S.No	INGREDIENTS	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}	F_{13}
1	Calcitriol	-	-	-	-	-	0.375 mcg	0.375 mcg	0.375 mcg	0.375 mcg	0.375 mcg	0.375 mcg	0.375 mcg	0.375 mcg
2	Calcium carbonate	1275.6	1275.6	1275.6	1275.6	1275.6	1275.6	1275.6	1275.6	1275.6	1275.6	1275.6	1275.6	1275.6
3	CCS	25	30	30	30	30	25	30	30	25	30	15	15	15
4	MCC	66	61	51	61	61	66	61	51	55.7	50.7	23.52	21.34	16.32
5	PVP	30	25	35	-	-	30	25	35	30	25	25	25	25
6	HPMC	-	-	-	25	-	-	-	-	-	-	-	-	-
7	DCP	-	-	-	-	25	-	-	-	-	-	-	-	-
8	Starch	-	-	-	-	-	-	-	-	-	-	2.18	4.36	2.18
9	BHA	-	-	-	-	-	-	-	-	0.3	0.3	0.3	0.3	0.3
10	BHT	-	-	-	-	-	-	-	-	0.3	0.3	0.3	0.3	0.3
11	Soyabean oil	-	-	-	-	-	-	-	-	10	10	10	10	10
12	Starch for paste	-	-	-	-	-	-	-	-	-	-	40	40	40
13	MCC RQ102	14.4	14.4	14.4	14.4	14.4	14.4	14.4	14.4	14.4	14.4	14.4	14.4	21.6
14	CCS	25	30	30	30	30	25	30	30	25	30	30	30	30
15	SSG	48	48	48	48	48	48	48	48	48	48	48	48	48
16	Talc	8	8	8	8	8	8	8	8	8	8	8	8	8
17	MGS	8	8	8	8	8	8	8	8	8	8	8	8	8

Serial numbers 1-13 are inter-granular ingredients and from serial number 13-17 are extra-granular ingredients.

API – Active pharmaceutical ingredient

SSG - Sodium starch glycolate

MCC - Microcrystalline cellulose

CCS - Cross carmallose sodium

MGS - Magnesium state

BHA- Butylated hydroxy anisole

BHT- Butylated hydroxy toluene

HPMC- Hydroxy propyl methyl cellulose
DCP- Di-calcium phosphate
PVP- Polyvinyl pyrolidine

FORCED DEGRADATION STUDY

Forced degradation study was done to get know how of various degradation pathways of API & oxidation was found to be major degradation pathway.

Table 3: PROTOCOL FOR FORCED DEGRADATION STUDIES

HYDROLYSING MEDIA	MEDIA USED
Acid hydrolysis	HCl conc.
Base hydrolysis	NaOH/KOH (conc.)
Oxidation	H_2O_2
Water hydrolysis	Water only

Aqueous granulation ($F_{9\text{-}13}$) comprises use of starch paste as binder and non aqueous granulation employs the use of isopropyl alcohol, methylene dichloride along with combination of BHA and BHT in soya bean oil.

Hardness of Calcitriol tablets of each batch was determined using Rimek hardness tester. *In-vitro* disintegration time was carried out using USP- disintegration test apparatus. Disintegration time of both reference product and batches was measured. It uses 6 glass tubes that are open at the top, and held against a 10 mesh screen at the bottom end of the basket rack assembly which operates at a frequency of 28 to 32 cycles per minute. One calcitriol tablet was placed in each tube and the basket assembly was positioned in 900 ml of water maintained at 37 ± 2ºC, in such a way that the tablets remain 2.5 cm below the surface of the liquid on their upward movement and descend not closer than 2.5 cm from the bottom of the beaker. The end point of disintegration was taken as the disappearance of the last tablet fragment in the tube. Loss on drying was measured using Sartorius LOD machine. Assay was determined as per United States pharmacopoeia.

RESULT AND DISCUSSION

Combination of aqueous and non aqueous granulations was effective in stabilization of calcitriol in tablet dosage form. BHA, BHT and soyabean oil prevent oxidative degradation of calcitriol and starch impart better flow.

Table 4: Results for Assay and Content Uniformity

Formulation code	ASSAY (%)	Content uniformity (%)*
F_1	---	100.23
F_2	---	99.99

F_3	---	100.02
F_4	---	99.74
F_5	---	98.87
F_6	Assay fails	99.68
F_7	Assay fails	99.34
F_8	Assay fails	100.07
F_9	99.21	99.56
F_{10}	99.37	99.69
F_{11}	101	99.83
F_{12}	Assay fails	99.00
F_{13}	101	99.73

*content uniformity is done only for calcium carbonate as this test is not required for trace elements and multivitamins.

Formulation F_9 was carried out with antioxidants BHA, BHT and medium chain triglyceride soyabean oil. Assay was found within limits but flow was not proper. Formulation F_{10} was combination of aqueous and non aqueous granulations which imparts good flow along with stabilization of calcitriol.

Table 5*: In-vitro* drug release studies of calcium carbonate portion of calcitriol tablets

CALCIUM CARBONATE PORTION									
Formulation F_{11}									
Dissolution: USP Type II / 900 ml/0.1 n HCl/37.5°C/50RPM									
Time interval (mins)	**1***	**2***	**3***	**4***	**5***	**6***	**Mean**	**SD**	**RSD**
0	0	0	0	0	0	0	0	0	0
5	55	62	63	58	59	61	60	2.94	4.93
15	83	86	89	91	88	83	87	3.27	3.77
30	95	97	96	98	99	97	97	1.41	1.46
45	99	101	100	102	103	97	100	2.16	2.15

***Percentage drug release.

Figure 2: Calcium release from formulated tablets

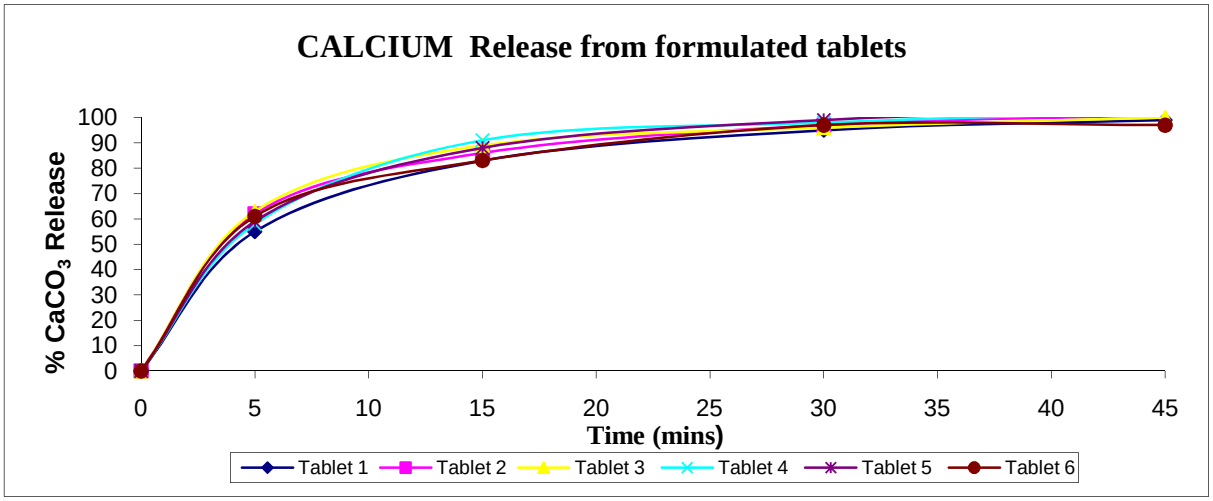
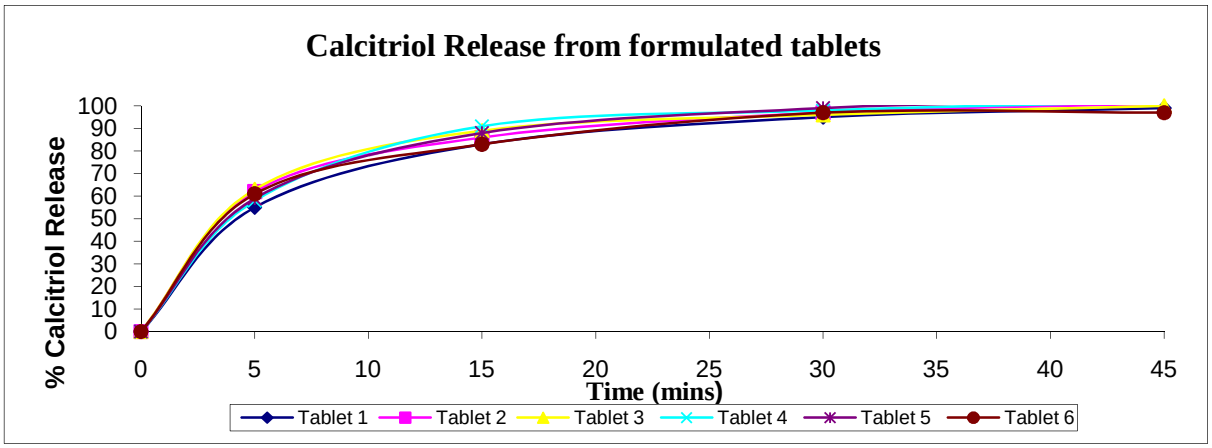


Table 6: *In-vitro* drug release studies of calcitriol portion of calcitriol tablets

CALCITRIOL PORTION									
Formulation F_{11}									
Dissolution: USP Type II / 900 ml/0.1 n HCl/37.5°C/50RPM									
Time interval (mins)	**1***	**2***	**3***	**4***	**5***	**6***	**Mean**	**SD**	**RSD**
0	0	0	0	0	0	0	0	0	0
5	18	22	19	20	27	19	21	3.31	15.90
15	75	77	79	81	83	77	79	2.94	3.74
30	89	90	88	87	83	88	86	2.43	2.82
45	94	98	98	99	99	99	98	1.94	1.98

***** Percentage drug release.

Figure 2: Calcitriol release from formulated tablet.



Short term stability study was performed for formulation F_{11} (optimized batch) at 40±5ºC/75±5%RH for period of 1 month. The samples were analyzed for percent drug release, friability, thickness, hardness and drug content.

CONCLUSION

In the present study, an attempt has been made to stabilize calcitriol in tablet dosage form using medium chain triglycerides and two stage granulation. Use of starch for granulation and antioxidants in soyabean oil; results in better flow of blend and stabilization of calcitriol in tablet dosage form. Stability studies for 1 month on formulation F_{11} were analysed for percent drug release, friability, thickness, hardness and drug content. No appreciable difference was observed in physical parameters as well as in % drug release. Among the various formulations studied, formulation F_{11} showed promising results like better flow of blend and stabilized API. Hence further studies like pharmacokinetic, pharmacodynamic and clinical trials can be performed to develop a marketed formulation.

REFERENCES

1. Rawlins EA. Bentley's text book of pharmaceutics. 8th ed. Bailliere Tindall, London. 2001; 270-97.
2. http:www.medicines.org.uk/
3. http://www.drugbank.ca/
4. British Pharmacopoeia 2009 Volume I&II. Monographs: Medicinal and Pharmaceutical substances monograph 0883.
5. Catherine M, Eric S. Therapeutic combination of vitamin and calcium in unitary galenic tablet form, a method of obtaining it and use thereof. US Patent no-6716454 B_2. 2004.
6. Benson AM, Thomas SK. Combined calcium and vitamin D suppliments.US Patent no-6509326 B_1.2003.
7. Shojaei AH, Ibharim SA, Burnside BA. Oral capsule formulation with increased physical stability. US Patent no-7011846 B_2.2006.
8. Barak F, Rosenberger, Moldavski, Lerner I. Sublingual dosage form comprising vitamin D analogue in particular calcitriol. US Patent no-0009793.2005.
9. Burnside BA, Henry F, Xiaodi G, Kun CR. Solid oral dosage form. US Patent no-6793934 B_1.2004.
10. Pasi M, Ann-Sophie L, Kauko L, Jouko Y. Influence of granulation and compression process

variables on flow rate of granules and on tablet properties, with special reference to weight variation. Inter J Pharm 1993; 102**:** 111-125.