ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

Stability studies of hydralazine hydrochloride orodispersible formulations

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Article History:

Received on: 03.07.2019
Revised on: 18.10.2019
Accepted on: 26.10.2019

Keywords:

Hydralazine Hydrochloride, Mouth dissolving tablets, Fast dissolving oral thin films

ABSTRACT

Solid dosage forms also have a impervious difficulties in patients especially for geriatric and paediatric patients.Dysphagia is common among all age groups. Orodispersible formulations (Fast dissolving tablets & Fast dissolving oral thin films) constitute an inventive dosage form that overcome the problems swallowing and provides speedy onset of action. The objective of present study was to formulate orodispersible formulations of Hydralazine HCL by different methods (Direct compression method, Sublimation method and solvent casting method). Based on physiochemical evaluations F9 (Direct compression method),SF9 (Sublimation method) for Fast dissolving tablets and H2 formulations (Solvent casting method) for Fast dissolving oral thin films were found optimized formula. The optimized formula were kept for stability under long term, accelerated and intermediate conditions for the study period of six months as per ICH guidelines.Based on stability reports the H2 formulations (Fast dissolving oral thin films) got a better drug release than Fast dissolving tablets.

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ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i1.1788

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INTRODUCTION

A mouth dissolving or disintegrating system can be defined as a novel dosage form for oral administration, which when placed in mouth, disintegrates rapidly or dissolves in saliva, within a few seconds. A mouth dissolving tablet usually dissolves in oral cavity within 15 seconds to 3 minutes.

Dysphagia, or difficulty in swallowing, is common among all age groups. Dysphagia is common in about 35% of the general population, as well as an additional 30-40% of elderly patients and 18-22% of all persons in long-term care facilities. This segment of a formulation is specially designed for dysphagia, geriatric, pediatric, bed-ridden, traveling, and psychotic patients who are unable to swallow or refuse to swallow conventional oral formulations.

Mouth dissolving tablets (MDTs) also called orodispersible, orally disintegrating tablets, quick-dissolving tablets, fast melt tablets, rapid disintegrating tablets, and freeze-dried wafers (Lindheimer *et al.*, 2008).

Criteria for mouth dissolving tablets

1. Water is not required to swallow and should dissolve or disintegrate in the mouth within a few seconds
2. Have a pleasing mouthfeel

Table 1: Stability condition chart

Intended Storage Condition	Minimum time period covered by data at submission	ICH Test Temperature and Humidity
Long Term	6 Months	25±2°C/60±5%RH
Intermediate	6 Months	30±2°C/65±5%RH
Accelerated	6 Months	40±2°C/75±5%RH

Table 2: Formulation of Hydralazine Hydrochloride mouth dissolving tablets by Direct compression method

S.No	Ingredients	Formulation code (Amount per tablet in mg)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Hydralazine Hcl	50	50	50	50	50	50	50	50	50
2	Croscarmellose sodium	8	10	12	-	-	-	-	-	-
3	Crospovidone	-	-	-	8	10	12	-	-	-
4	Sod. Starch glycolate	-	-	-	-	-	-	8	10	12
5	Aspartame	5	5	5	5	5	5	5	5	5
6	Mannitol	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
7	Magnesium Stearate	2	2	2	2	2	2	2	2	2
8	Mcc	83	81	79	83	81	79	83	81	79
9	Talc	2	2	2	2	2	2	2	2	2
10	Tween 80	6	6	6	6	6	6	6	6	6

Table 3: Formulation of Hydralazine Hydrochloride mouth dissolving tablets of by Sublimation method

S.No	Ingredients	Formulation code (amount per tablet in mg)								
		SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8	SF9
1	Hydralazine HCL	50	50	50	50	50	50	50	50	50
2	Crospovidone	6	8	10	-	-	-	-	-	-
3	Croscarmellose sodium	-	-	-	6	8	10	-	-	-
4	Sod. Starch glycolate	-	-	-	-	-	-	6	8	10
5	Aspartame	5	5	5	5	5	5	5	5	5
6	Mannitol	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S	Q. S
7	Magnesium state	2	2	2	2	2	2	2	2	2
8	Camphor	2	4	6	2	4	6	2	4	6
9	MCC	83	80	77	83	80	77	83	80	77
10	Talc	2	2	2	2	2	2	2	2	2
11	Tween 80	6	6	6	6	6	6	6	6	6

Table 4: Formulation of Hydralazine Hydrochloride fast dissolving oral thin films of by Solvent casting method

S.No	Ingredients	HPMC(H)			Pectin(P)			Sodium alginate(S)		
		H1	H2	H3	P4	P5	P6	S7	S8	S9
1	Hydralazine Hydrochloride (mg)	50	50	50	50	50	50	50	50	50
2	Polymer (mg)	150	250	350	150	250	350	150	250	350
3	DMSO (ml)	0.3	0.5	0.7	0.3	0.5	0.7	0.3	0.5	0.7
4	Glycerin (ml)	0.3	0.5	0.7	0.3	0.5	0.7	0.3	0.5	0.3
5	Water (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
6.	Span 60	6	6	6	6	6	6	6	6	6

Table 5: Stability study for Hydralazine Hydrochloride MDTs of formulation F9 prepared by Direct compression method Stored at 40°C ± 2°C and 75%±5% RH

S.No	Parameters	Initial	Stored at 40°C ± 2°C and 75%±5% RH In month					
			1	2	3	4	5	6
1	Description	White colour	White colour	White colour	White colour	White colour	White colour	White colour
2	Average weight (mg)	201	201	201	202	202	202	202
3	Friability(%)	0.26	0.26	0.28	0.29	0.27	0.26	0.31
4	Hardness (kg/cm2)	3.7	2.6	2.6	2.5	2.6	2.6	2.5
5	Disintegration time (sec)	26	26	27	27	26	26	27
6	Drug content (%)	99.98	99.97	99.95	99.94	99.80	99.16	99.03

(Kumar and Ganapathy, 2018; Muthukumar and Ganapathy, 2018)

Table 6: Comparative in-vitrodissolution profile of MDTs of Hydralazine HCL (F9) prepared by Directcompression method, before and after storage at 40°C±2°C and 75%±5% RH

Time in minutes	Cumulative % of drug released (±S.D)						
	Initial	1^{st} month	2^{nd} month	3^{rd} month	4^{th} month	5^{th} month	6^{th} month
2	14.64 ± 1.25	14.68 ± 1.34	14.45 ± 1.22	14.34 ± 1.20	14.28 ± 5.42	13.55 ± 2.03	14.79 ± 5.26
4	44.05 ± 1.47	44.01 ± 2.17	43.98 ± 1.40	43.68 ± 1.31	43.31 ± 1.477	43.67 ± 2.60	44.66 ± 1.79
6	72.52 ± 0.65	72.50 ± 0.81	71.23 ± 0.44	72.01 ± 0.12	71.50 ± 0.61	72.33 ± 0.78	72.63 ± 0.97
8	83.29 ± 0.69	83.29 ± 0.67	82.18 ± 0.58	83.14 ± 0.24	82.86 ± 0.14	83.16 ± 0.62	82.44 ± 0.74
10	89.78 ± 0.58	89.70 ± 0.86	89.56 ± 0.72	89.10 ± 0.24	89.70 ± 0.13	89.84 ± 0.22	89.68 ± 0.52
12	90.20 ± 0.58	90.10 ± 0.24	90.01 ± 0.64	89.92 ± 0.82	89.65 ± 0.35	89.30 ± 0.12	89.42 ± 0.52

(Kumar and Ganapathy, 2018; Muthukumar and Ganapathy, 2018)

Table 7: Stability study for Hydralazine Hydrochloride MDTs of formulation F9 prepared by Direct compression method Stored at 30°C ± 2°C and 65%±5% RH

S.No	Parameters	Initial	Stored at 25°C ± 2°C and 60%±5% RH In month					
			1	2	3	4	5	6
1	Description	White colour	White colour	White colour	White colour	White colour	White colour	White colour
2	Average weight (mg)	200	201	200	201	202	201	202
3	Friability (%)	0.25	0.26	0.27	0.28	0.26	0.25	0.30
4	Hardness (kg/cm2)	3.5	2.5	2.6	2.5	2.5	2.6	2.4
5	Disintegration time (sec)	25	25	26	26	25	25	26
6	Drug content (%)	99.97	99.96	99.95	99.94	99.78	99.14	99.01

(Kumar and Ganapathy, 2018; Muthukumar and Ganapathy, 2018)

Table 8: Comparative *in-vitro* dissolution profile of MDTs of Hydralazine HCL (F9) prepared by Direct compression method, before and after storage at 25°C±2°C and 60%±5% RH

Time in minutes	Cumulative % of drug released (±S.D)						
	initial	1^{st}month	2^{nd}month	3^{rd} month	4^{th} month	5^{th} month	6^{th} month
2	14.64 ± 1.25	14.68 ± 1.34	14.45 ± 1.22	14.34 ± 1.20	14.28 ± 5.42	13.55 ± 2.03	14.79 ± 5.26
4	44.02 ± 1.47	44.00 ± 2.17	43.94 ± 1.40	43.62 ± 1.31	43.28 ± 1.477	43.62 ± 2.60	44.60 ± 1.79
6	72.50 ± 0.65	72.46 ± 0.81	71.20 ± 0.44	72.00 ± 0.12	71.46 ± 0.61	72.30 ± 0.78	72.60 ± 0.97
8	83.25 ± 0.69	83.27 ± 0.67	82.10 ± 0.58	83.12 ± 0.24	82.82 ± 0.14	83.12 ± 0.62	82.40 ± 0.74
10	89.76 ± 0.58	89.66 ± 0.86	89.52 ± 0.72	89.06 ± 0.24	89.68 ± 0.13	89.80 ± 0.22	89.64 ± 0.52
12	90.16 ± 0.58	90.04 ± 0.24	90.00 ± 0.64	89.88 ± 0.82	89.60 ± 0.35	89.25 ± 0.12	89.40 ± 0.52

(Kumar and Ganapathy, 2018; Muthukumar and Ganapathy, 2018)

3. Acceptable taste-masking property

4. Be compatible with taste masking and other excipients

5.Allow high drug loading

6.Leave minimal or no residue in mouth after oral administration

7.Have sufficient strength to withstand the rigors of the manufacturing process and post-manufacturing handling

8.Exhibit low sensitivity to environmental conditions such as humidity and temperature

9.Be adaptable and amenable to existing processing and packing machinery

10.Allow the manufacture of tablets using conventional processing and packing equipment at low cost

Advantages of mouth dissolving tablets

1. Ease of administration to patients who cannot swallow, such as the elderly, stroke victims and bedridden patients, patients who should not swallow, such as renal failure patients, and who refuse to swallow, such as pediatrics, geriatrics and psychiatrists patients
2. Patients compliance for disabled, bedridden patients, for traveling and for busy peoples who

Table 9: Stability study for Hydralazine Hydrochloride MDTs of formulation F9 prepared by Direct compression method Stored at 30°C ± 2°C and 65%±5% RH

S.No	Parameters	Initial	Stored at 30°C ± 2°C and 65%±5% RH In month					
			1	2	3	4	5	6
1	Description	White colour	White colour	White colour	White colour	White colour	White colour	White colour
2	Average weight (mg)	200	201	200	201	201	201	201
3	Friability(%)	0.24	0.25	0.26	0.28	0.24	0.25	0.29
4	Hardness (kg/cm2)	3.0	2.4	2.4	2.5	2.5	2.4	2.2
5	Disintegration time (sec)	25	24	25	26	24	22	25
6	Drug content (%)	99.96	99.94	99.93	99.90	99.76	99.10	99.00

(Kumar and Ganapathy, 2018; Muthukumar and Ganapathy, 2018)

Table 10: Comparative *in-vitro* dissolution profile of MDTs of Hydralazine HCL (F9) prepared by Direct compression method, before and after storage at 30°C±2°C and 65%±5% RH

Time in minutes	Cumulative % of drug released (±S.D)						
	Initial	1^{st} month	2^{nd} month	3^{rd} month	4^{th}month	5^{th}month	6^{th} month
2	14.60 ± 1.25	14.64 ± 1.34	14.40 ± 1.22	14.30 ± 1.20	14.25 ± 5.42	13.51 ± 2.03	14.75 ± 5.26
4	44.00 ± 1.47	43.98 ± 2.17	43.90 ± 1.40	43.64 ± 1.31	43.26 ± 1.477	43.60 ± 2.60	44.62 ± 1.79
6	72.48 ± 0.65	72.44 ± 0.81	71.20 ± 0.44	72.00 ± 0.12	71.42 ± 0.61	72.26 ± 0.78	72.54 ± 0.97
8	83.20 ± 0.69	82.25 ± 0.67	82.10 ± 0.58	82.10 ± 0.24	82.70 ± 0.14	83.10 ± 0.62	82.40 ± 0.74
10	89.70 ± 0.58	89.60 ± 0.86	89.52 ± 0.72	89.06 ± 0.24	89.66 ± 0.13	89.80 ± 0.22	89.62 ± 0.52
12	90.16 ± 0.58	90.04 ± 0.24	90.00± 0.64	89.86 ± 0.82	88.65 ± 0.35	88.30 ± 0.12	89.36 ± 0.52

(Kumar and Ganapathy, 2018; Muthukumar and Ganapathy, 2018)

don't have ready to access to water

3. Good mouthfeel property of mouth dissolving drug delivery system helps to change the basic view of medication drugs
4. The convenience of administration and accurate dosing as compared to liquid formulations
5. The benefit of liquid medication in the form of solid preparation
6. More rapid drug absorption from the pregastric area i.e., mouth, pharynx, and esophagus which may produce rapid onset of action
7. Pre-gastric mucosa can result in improved bioavailability, reduce the dose and improved clinical performance by reducing side effects
8. Improved taste without any residue in mouth after the disintegration
9. The risk of choking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety
10. Beneficial in cases such as heart attack, motion sickness (kinetosis), sudden episodes of allergic attack or coughing, where an ultra-rapid onset of action required

Table 11: Stability study for Hydralazine Hydrochloride MDTs offormulation SF9 prepared by Sublimation method Stored at 40°C±2°C and75%±5% RH

S.No	Parameters	Initial	Stored at 40°C±2°C and 75%±5% RH In month					
			1	2	3	4	5	6
1	Description	White colour	White colour	White colour	White colour	White colour	White colour	White colour
2	Average weight (mg)	200	200	199.90	199.28	200	199.90	199.28
3	Friability (%)	0.20	0.20	0.20	0.20	0.20	0.20	0.20
4	Hardness (kg/cm2)	3.9	3.0	2.9	2.9	3.0	2.9	2.9
5	Disintegration time (sec)	13	13	14	15	13	14	15
6	Drug content (%)	99.99	99.90	99.82	99.80	99.90	99.82	99.80

(Kumar and Ganapathy, 2018; Muthukumar and Ganapathy, 2018)

Table 12: Comparative *in-vitro* dissolution profile of MDTs of Hydralazine HCl (SF9) prepared by Sublimation method, before and after storage at Stored at 40°C±2°C and 75%±5% RH

Time in minutes	Cumulative % of drug release (±S.D)						
	Initial	1^{st}month	2^{nd} month	3^{rd} month	4^{th} month	5^{th} month	6^{th} month
2	22.13 ± 0.25	22.01 ± 0.26	22.00 ± 0.14	21.88 ± 0.54	21.81 ± 0.58	22.48 ± 0.53	21.65 ± 0.49
4	57.38 ± 0.47	57.28 ± 0.40	57.04 ± 0.26	56.92 ± 0.24	57.67 ± 0.05	57.62 ± 0.67	56.75 ± 0.83
6	77.52 ± 0.15	77.50 ± 0.14	76.98 ± 0.11	76.62 ± 0.82	76.55 ± 0.62	76.85 ± 0.95	76.22 ± 0.63
8	89.20 ± 0.32	89.12 ± 0.24	88.92 ± 0.14	88.82 ± 0.45	89.37 ± 0.56	88.24 ± 0.48	88.32 ± 0.66
10	93.78 ± 0.98	93.44 ± 0.72	93.01 ± 0.26	92.42 ± 0.58	92.42 ± 0.52	92.01 ± 0.71	92.12 ± 0.55
12	98.20 ± 0.1	98.10 ± 0.14	97.92 ± 0.12	97.89 ± 0.18	97.63 ± 0.81	97.73 ± 0.84	97.28 ± 0.92

(Kumar and Ganapathy, 2018; Muthukumar and Ganapathy, 2018)

Durable and sufficient strength to withstand the rigors of the manufacturing process and handling

A fast-dissolving buccal film drug delivery system is a film containing an active ingredient that fastly dissolves or fastly disintegrates in the saliva, within a few seconds without the need for water or chewing (Irfan *et al.*, 2016). Fast dissolving films for oral administration was a novel approach for patients who experience difficulties in swallowing tablets or capsules. Geriatric, pediatric, and dysphasia patients associated with many medical conditions face a problem of difficulty in swallowing solid dosage forms. (Kumar and Bhagyashree, 2013). One study showed that 26% of 1576 patients experienced difficulty in swallowing tablets (Arya *et al.*, 2010). Oral fast-dissolving drug-delivery systems were developed in the late 1970's to overcome the problem of difficulty in swallowing solid dosage forms (Khatoon *et al.*, 2013). These systems consist of oral dispersible tablets (ODT) that disintegrate and dissolve quickly in the oral cavity. Oral strips and oral films which rapidly dissolve under the tongue or buccal cavity could also improve the dissolution of the poorly soluble drug. It gives the residence time of the dosage form at the site of absorption, hence increase the bioavailability. It gives ease of administration to paediatric, geriatric patients, and also to the patients who are mentally retarded, disabled, or non-cooperative (Madhavi, 2013). Hydralazine hydrochloride is a medica-

Table 13: Stability study for Hydralazine Hydrochloride MDTs of formulation SF9 prepared by Sublimation method Stored at 25°C±2°C and 60%±5% RH

S.No	Parameters	Initial	Stored at 25°C±2°C and 60%±5% RH In month					
			1	2	3	4	5	6
1	Description	White colour	White colour	White colour	White colour	White colour	White colour	White colour
2	Average weight (mg)	199.96	199.90	199.82	199.20	199.92	199.76	199.14
3	Friability (%)	0.18	0.19	0.18	0.16	0.19	0.18	0.20
4	Hardness (kg/cm2)	3.6	2.9	2.8	2.8	2.8	2.6	2.8
5	Disintegration time (sec)	11	12	12	13	11	11	14
6	Drug content (%)	99.90	99.86	99.78	99.72	99.80	99.72	99.70

(Kumar and Ganapathy, 2018; Muthukumar and Ganapathy, 2018)

Table 14: Comparative *in-vitro* dissolution profile of MDTs of Hydralazine HCl (SF9) prepared by Sublimation method, before and after storage at Stored at 25°C±2°C and 60%±5% RH

Time in minutes	Cumulative % of drug release (±S.D)						
	Initial	1^{st} month	2^{nd} month	3^{rd} month	4^{th} month	5^{th} month	6^{th} month
2	22.10 ± 0.25	21.98 ± 0.26	21.90 ± 0.14	21.82 ± 0.54	21.71 ± 0.58	22.40 ± 0.53	21.55 ± 0.49
4	57.24 ± 0.47	57.18 ± 0.40	56.82 ± 0.26	56.72 ± 0.24	57.10 ± 0.05	57.15 ± 0.67	56.25 ± 0.83
6	77.40 ± 0.15	77.36 ± 0.14	76.82 ± 0.11	76.42 ± 0.82	76.35 ± 0.62	76.70 ± 0.95	76.10 ± 0.63
8	88.98 ± 0.32	89.02 ± 0.24	88.72 ± 0.14	88.62 ± 0.45	89.17 ± 0.56	88.14 ± 0.48	88.12 ± 0.66
10	93.28 ± 0.98	93.14 ± 0.72	92.90 ± 0.26	92.12 ± 0.58	92.02 ± 0.52	91.80 ± 0.71	92.02 ± 0.55
12	98.10 ± 0.1	97.90 ± 0.14	97.66 ± 0.12	97.54 ± 0.18	97.38 ± 0.81	97.24 ± 0.84	97.18 ± 0.92

(Kumar and Ganapathy, 2018; Muthukumar and Ganapathy, 2018)

tion used to treat high blood pressure and heart failure. This includes high blood pressure in pregnancy. Hydralazine hydrochloride acts as a vasodilator. The drug undergoes extensive first-passed metabolism with a plasma half-life of 2 - 8 h. Hydralazine hydrochloride has a low bio-availability of 50%, and the efficacy of protein binding is 90 %.

MATERIALS AND METHODS

The drug Hydralazine Hydrochloride was obtained from Octopus pharmaceuticals, Chennai. Croscarmellose sodium, Crospovidone, Sodium starch glycolate, Aspartame, Mannitol, Magnesium stearate, Microcrystalline cellulose, Talc, Camphor were procured from Himedia Ltd., Goa. Hydroxyl propyl methylcellulose (Hi-Media Laboratories Limited, Mumbai.), Pectin (Hi-Media Laboratories Limited, Mumbai), Sodium Alginate (Merck Limited, Mumbai), Dimethyl sulfoxide (Merck Limited, Mumbai), Glycerine (Microfine Chemicals, New Delhi), Sodium Lauryl Sulfate (Microfine Chemicals, New Delhi) and all other excipient used were analytical grade.

Preparation of Orodispersible tablets by direct compression method

Orodispersible tablets of Hydralazine hydrochloride were prepared by direct compression method using super disintegrants such as crospovidone,

Table 15: Stability study for Hydralazine Hydrochloride MDTs of formulation SF9 prepared by Sublimation method Stored at 30°C±2°C and 65%±5% RH

S.No	Parameters	Initial	Stored at 30°C±2°C and 65%±5% In month					
			1	2	3	4	5	6
1	Description	White colour	White colour	White colour	White colour	White colour	White colour	White colour
2	Average weight (mg)	200	200	199.90	199.28	200	199.90	199.28
3	Friability (%)	0.19	0.18	0.19	0.19	0.18	0.20	0.18
4	Hardness (kg/cm2)	3.5	2.8	2.6	2.6	2.8	2.8	2.6
5	Disintegration time (sec)	12	11	13	14	11	12	13
6	Drug content (%)	99.92	99.84	99.60	99.74	99.66	99.72	99.64

(Kumar and Ganapathy, 2018; Muthukumar and Ganapathy, 2018)

Table 16: Comparative *in-vitro* dissolution profile of MDTs of Hydralazine HCl (SF9) prepared by Sublimation method, before and after storage at Stored at 30°C±2°C and 65%±5% RH

Time in minutes	Cumulative % of drug release (±S.D)						
	Initial	1^{st} month	2^{nd}month	3^{rd} month	4^{th} month	5^{th} month	6^{th} month
2	22.10 ± 0.25	21.96 ± 0.26	21.90 ± 0.14	21.74 ± 0.54	21.68 ± 0.58	21.30 ± 0.53	21.24± 0.49
4	57.22 ± 0.47	57.14 ± 0.40	56.84 ± 0.26	56.72 ± 0.24	56.47 ± 0.05	56.32 ± 0.67	56.25± 0.83
6	77.28 ± 0.15	77.10 ± 0.14	76.58 ± 0.11	76.42 ± 0.82	76.35 ± 0.62	76.25 ± 0.95	76.02 ± 0.63
8	89.16 ± 0.32	89.10 ± 0.24	88.82 ± 0.14	88.62 ± 0.45	89.27 ± 0.56	88.14 ± 0.48	88.02 ± 0.66
10	93.68 ± 0.98	93.34 ± 0.72	92.90 ± 0.26	92.32 ± 0.58	92.22 ± 0.52	92.00 ± 0.71	91.90 ± 0.55
12	98.10 ± 0.1	98.06 ± 0.14	97.82 ± 0.12	97.79 ± 0.18	97.60 ± 0.81	97.54 ± 0.84	97.24 ± 0.90

(Kumar and Ganapathy, 2018; Muthukumar and Ganapathy, 2018)

croscarmellose sodium, and sodium starch glycolate in varying ratios. All the materials were passed through the mesh number of 60 meshes before mixing for uniformity in particle size. The drug and microcrystalline cellulose were mixed using a glass mortar of pestle in a small portion of both at each time, which blended to get a uniform mixture and kept aside. Then the other ingredients were weighed and mixed in a geometrical order in which the tablets were compressed using an 8mm size punch to get 200 mg weight using ten stations Rimek tablet punching machine (Shukla, 2009).

Preparation of Mouth Dissolving Tablet by Sublimation method

Tablets were prepared by using camphor in different ratios. All the ingredients were passed through #60 mesh separately. Then the ingredients were weighed and mixed in geometrical order, and the tablets were compressed using an 8mm size punch to get 200 mg weight using ten stations Rimek tablet punching machine. The compressed tablets were subjected to sublimation at 60 °C for 1 hour. Compositions of different formulations were prepared by the sublimation technique (Shukla, 2009).

Preparation of Buccal Films

Nine batches of drug-loaded buccal films were prepared using the drug with different polymer (HPMC, pectin, sodium alginate) in different Drug: Polymer

Table 17: Stability Studies for Hydralazine Hydrochloride Fast dissolving oral thin Film of formulation [H2]

Parameter	25±20C& RH 60±5%	40±20C& RH 75±5%	30±20C& RH 65±5%
Visual Appearance	Transparent	Transparent	Transparent
Initial	No change	No change	No change
At the end of 1st month	No change	No change	No change
At the end of 2nd month	No change	No change	No change
At the end of 3rd month	No change	No change	No change
At the end of 6th month	No change	No change	No change
Colour	Dull white	Dull white	Dull white
Initial	No change	No change	No change
At the end of 1st month	No change	No change	No change
At the end of 2nd month	No change	No change	No change
At the end of 3rd month	No change	No change	No change
At the end of 6th month	No change	No change	No change
Texture	Smooth	Smooth	Smooth
Initial	No change	No change	No change
At the end of 1st month	No change	No change	No change
At the end of 2nd month	No change	No change	No change
At the end of 3rd month	No change	No change	No change
At the end of 6th month	No change	No change	No change
Drug content (%)			
Initial	98.82	98.82	98.64
At the end of 1st month	98.82	98.55	98.45
At the end of 2nd month	98.05	97.87	97.60
At the end of 3rd month	97.84	97.54	97.42
At the end of 6th month	97.50	97.27	97.12

(Kumar and Ganapathy, 2018; Muthukumar and Ganapathy, 2018)

Table 18: Stability Study for Hydralazine Hydrochloride Fast dissolving oral thin Film of formulation [H2] stored at 25±20C & 60±5%RH

Time in minutes	% Drug Diffused H2 Formulation (HPMC) 25±20C& RH 60±5%						
	Initial	1^{st} month	2^{nd} month	3^{rd} month	4^{th} month	5^{th} month	6^{th} month
10	14.10 ± 0.26	14.08 ± 0.22	14.06 ± 0.20	14.04 ± 0.26	14.02 ± 0.22	13.98 ± 0.22	13.95 ± 0.21
20	28.16 ± 0.43	28.15 ± 0.42	28.13 ± 0.43	28.10 ± 0.41	28.08 ± 0.43	28.04 ± 0.42	27.98 ± 0.40
30	45.78 ± 0.21	45.76 ± 0.20	45.72 ± 0.21	45.70 ± 0.24	45.68 ± 0.21	45.66 ± 0.26	45.62 ± 0.23
40	69.49 ± 0.09	69.45 ± 0.08	69.40 ± 0.09	69.38 ± 0.12	69.35 ± 0.14	69.30 ± 0.09	69.09 ± 0.14
50	87.50 ± 0.72	87.46 ± 0.70	87.45 ± 0.72	87.40 ± 0.70	87.38 ± 0.74	87.35 ± 0.72	87.32 ± 0.74
60	98.80 ± 0.11	98.78 ± 0.10	98.76 ± 0.11	98.74 ± 0.14	98.72 ± 0.12	98.70 ± 0.14	98.68 ± 0.13

(Kumar and Ganapathy, 2018; Muthukumar and Ganapathy, 2018)

Table 19: Stability Study for Hydralazine Hydrochloride Fast dissolving oral thin Film of formulation [H2] stored at 40±20C& RH 75±5%

Time in minutes	% Drug Diffused H2 Formulation (HPMC) 40±20C& RH 75±5%						
	Initial	1^{st} month	2^{nd} month	3^{rd} month	4^{th} month	5^{th} month	6^{th}month
10	14.15 ± 0.24	14.12 ± 0.26	14.10 ± 0.24	14.04 ± 0.23	14.02 ± 0.23	13.98 ± 0.26	13.84 ± 0.25
20	28.20 ± 0.42	28.18 ± 0.43	28.14 ± 0.40	28.13 ± 0.41	28.08 ± 0.43	28.04 ± 0.43	27.85 ± 0.40
30	45.78 ± 0.20	45.75 ± 0.28	45.68 ± 0.21	45.60 ± 0.22	45.58 ± 0.25	45.48 ± 0.21	45.18 ± 0.26
40	69.18 ± 0.16	69.16 ± 0.09	69.14 ± 0.09	69.09 ± 0.14	69.05 ± 0.03	68.86 ± 0.09	68.50 ± 0.12
50	87.52 ± 0.70	87.50 ± 0.73	87.45 ± 0.72	87.40 ± 0.76	87.35 ± 0.78	86.34 ± 0.72	86.12 ± 0.75
60	98.86 ± 0.10	98.82 ± 0.16	98.76 ± 0.11	98.70 ± 0.15	98.56 ± 0.14	98.26 ± 0.18	97.9 2± 0.14

(Kumar and Ganapathy, 2018; Muthukumar and Ganapathy, 2018)

Table 20: Stability Study for Hydralazine Hydrochloride Fast dissolving oral thin Film of formulation [H2] stored at 30±20C& RH 65±5%

Time	% Drug Diffused H2 Formulation (HPMC) 30±20C& RH 65±5%						
	Initial	1^{st} month	2^{nd} month	3^{rd} month	4^{th} month	5^{th} month	6^{th} month
10	14.28 ± 0.26	14.20 ± 0.26	14.14 ± 0.26	14.04 ± 0.26	13.90 ± 0.26	13.78 ± 0.26	13.60 ± 0.26
20	28.26 ± 0.43	28.20 ± 0.43	28.14 ± 0.43	28.06 ± 0.43	27.84 ±0.43	27.60 ± 0.43	27.48 ± 0.43
30	45.80 ± 0.21	45.74 ± 0.21	45.68 ± 0.21	45.46 ± 0.21	45.28 ± 0.21	45.08 ± 0.21	44.88 ± 0.21
40	69.46 ± 0.09	69.40 ± 0.09	69.30 ± 0.09	69.09 ± 0.09	68.96 ± 0.09	68.85 ± 0.09	68.60 ± 0.09
50	87.52 ± 0.72	87.45 ± 0.72	87.36 ± 0.72	87.15 ± 0.72	87.05 ± 0.72	86.94 ± 0.72	86.70 ± 0.72
60	98.96 ± 0.11	98.84 ± 0.11	98.76 ± 0.11	98.52 ± 0.11	98.24 ± 0.11	98.16 ± 0.11	98.02 ± 0.11

ratio (1:1, 1:3, and 1:5). The weighed quantity of polymer was dissolved in the calculated quantity of water and heated on a water bath. The calculated amount of drug was added to the above mixture and stirred well until a homogenous mixture was formed. Then the calculated amount of permeation enhancer and Glycerin were added. The resultant mixture was poured into a Petri dish and air-dried at room temperature for 24 h. The films were then peeled off from the Petri dish with the help of a knife and kept in a desiccator (Madhavi, 2013).

RESULTS AND DISCUSSION

Table 2 represented formula for MDTs of Hydralazine Hydrochloride using direct compression method.Based on evaluation parameters F9 formulation was selected as a optimized formula and kept in to stability at different conditions as per ICH guidelines mentioned in Table 1 . (Kumar and Ganapathy, 2018; Muthukumar and Ganapathy, 2018)

Table 3 represented the formula for MDTs of Hydralazine Hydrochloride using sublimation method.Based on evaluation parameters SF9 formulation was selected as a optimized formula and

kept in to stability at different conditions as per ICH guidelines mentioned in Table 1. (Kumar and Ganapathy, 2018; Muthukumar and Ganapathy, 2018)

Table 4 represented the formula for Fast dissolving oral thin films of Hydralazine Hydrochloride using solvent casting method.Based on physiochemical evaluations F9,SF9,H2 formulations were selected as a optimized formula and kept in to stability at different conditions as per ICH guidelines (Kumar and Ganapathy, 2018; Muthukumar and Ganapathy, 2018)

Stability Studies of mouth dissolving tablets F9 & SF9

Stability results represented in Table 5, Table 6, Table 8, Table 9, Table 10, Table 11, Table 12, Table 13, Table 14, Table 16, indicated that the optimized formulation F9 and SF9 show better stability under accelerated, intermediate, long term condition as per the ICH guidelines.

Stability studies for orodispersible tablets & Fast dissolving oral thin films

Stability is defined as the time-lapse during which the drug product retains the same property and characteristics that it possessed at the time of manufacture. This process being early development phases.

Instability in the modern formulation is often undetectable only after a considerable storage period under normal conditions. To assess the stability of a formulated product, it is usual to expose it to high-stress conditions to enhance deterioration, and therefore the time required for testing is reduced. Common high stresses are temperature and humidity. This will eliminate unsatisfactory formulation (Mazzo, 1998).

Strategy of stability testing

1. The study of drug decomposition kinetics
2. The development of stable dosage form
3. Establishment of the expiry date for a commercially available drug product is some of the needs of stability testing
4. Data from which study should be provided on at least 3 primary batches of the drug product
5. The batches should be manufactured to a minimum of a pilot scale.
6. An important point of view of the safety of the patient, patient relieves a uniform dose throughout the shelf life of the product.

Stability Studies of Fast dissolving oral thin films (H2)

The stability studies of HPMC [H2] Formulation of the buccal film was carried out for 6 months under long term, intermediate, accelerated conditions. The results represented in Table 17, Table 18, Table 19, Table 20. During this period, the formulation was stable and showed no significant changes in visual appearance, colour, texture, and drug content.

CONCLUSION

Mouth dissolving tablets

Based on stability results concluded that SF9 gives the results of an effective percentage of drug release of 97.28 ± 0.92 at 12minutes than F9 gives a drug release of 89.42±0.52 at 12 minutes.SF9 is indicating faster and maximum absorption at the site of administration than F9.

Fast dissolving oral thin films:

From this study, H2 concluded as an optimized and stable formulation from the results of evaluation & stability studies of Hydralazine Hydrochloride Fast dissolving oral thin films by solvent casting method.

Comparative study of mouth dissolving tablets vs. Fast dissolving oral thin films

1. Based on stability results concluded that SF9(Mouth dissolving tablets-sublimation method) gives the results of an effective percentage of drug release of 97.28 ± 0.92 at 12minutes (accelerated condition),97.18± 0.92(Long Term Condition),97.24± 0.90(Intermediate condition).
2. Based on stability results concluded that H2(Fast dissolving oral thin film-HPMC formulation) gives the results of an effective percentage of drug release of 97.92 ± 0.14 at 60seconds (accelerated condition), 98.68± 0.13 (Long Term Condition),98.02± 0.11(Intermediate condition).
3. Based on the stability results of mouth dissolving tablets (SF9) and Fast dissolving oral thin films (H2) formulations compare with the in-vitro studies, it showed that the Fast dissolving oral thinfilms(H2) got a better drug release than mouth dissolving tablets (SF9).
4. In Future, the work is considered for further development.

ACKNOWLEDGEMENT

The author would like to thanks my Guide Dr. R. Sundara Ganapathy, for his valuable guidance and inspiration for promoting this work. I would like to thank Karpagam Academy of Higher Education and KMCH College of Pharmacy for providing facilities for conducting the work.

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