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Fast Dissolving Tablets of Ergotamine Tartrate – A Noval Dosage Form

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Abstract

A vast variety of pharmaceutical research is directed at developing new dosage forms for oral administration. Most of these efforts have focused on either formulating novel drug delivery systems or increasing the patient compliance. Among the dosage forms developed for facilitating ease of medication, the orally disintegrating systems have been the favourite of product development scientists.

Formulation of mouth dissolving tablet is one of the recent advance in the novel drug delivery system, which gives advantages like increased bioavailability, reduced dose and improved clinical performance by reducing side effect. When put on tongue this tablet disintegrates instantaneously releasing the drug which dissolves or disperses in the saliva passes down into the stomach.

In such case bioavailability of drug is significantly greater than those observed from conventional tablet dosage form .

Ergotamine tartrate is an ergot alkaloid used to treat a migraine type headache. It acts on migraine by one of two proposed mechanism: 1) Action of 5-HT10 receptors located on intracranial blood vessels. 2) Action of 5 of -HT_{1D} receptors on sensory nerve ending of the trigeminal system. Plasma half life is about 2 hours. Plasma clearance, about 5 to 18 mL/min/kg (mean 11).

FDT will avoid missing out a dose even during travelling or other situations, where there is no access to water; offers a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with increased bioavailability.

Therefore, the present study was undertaken with an intention to develop fast disintegrating tablets (FDTs) of Ergotamine tartrate using crospovidone and croscarmellose sodium (superdisintegrants) with a view to provide a convenient means of administration to those patients suffering from difficulty in swallowing such as paediatric, geriatric, uncooperative mentally ill patients and patients who do not have ready to access water.

Key words *- Ergotamine tartrate, fast disintegrating tablet, bioavailability, Excipents.*

Introduction

Disease management of outdoor patients is mainly affected by patient compliance to the drug therapy, which in turn is governed by patient convenience. Failure to follow through with a treatment decision is one of the biggest causes of unsuccessful medical care. At present, different formulation options are available for various drugs, and hence, the decision is based on the most convenient dosage form for the patient, along with optimum therapeutic benefits.

A rapid dissolving tablet can be defined as a solid dosage form that can disintegrates into smaller granules which slowly dissolve in the mouth. The disintegration time for rapid dissolving tablet varies from a few seconds to more than a minute depending on the formulation and the size of the tablet. [4]

Due to the presence of superdisintegrants, it gets dissolved quickly, resulting in rapid absorption of drug which in turn provides rapid onset of action. Since absorption is taking place directly from mouth, so bioavailability of drug increases. Drug present in orodispersible tablets are also not suffering from first pass metabolism. This type of drug delivery is becoming popular day by day due to its numerous advantages

A effort to develop a novel type of tablet dosage form for oral administration i.e., one, which sintegrates/dissolves rapidly in saliva without the need for drinking water. This tablet disintegrates instantaneously or disperses in the saliva.[8]

Fast disintegrating drug delivery Systems are easy to administer and handle hence, leads to better

patient compliance. Usually, elderly people experience difficulty in swallowing the conventional dosage forms (tablets, capsules, solutions and suspensions) because of tremors of extremities and *dysphasia*. Fast Dissolving Delivery Systems may offer a solution for these problems

Objectives of the study:

In present work, studies will be carried out on the designing of fast dissolving tablet of Ergotamine Tartrate by direct compression method by using synthetic excipients, superdisintegrant addition and use of sugar based excipients.

- To improve patient compliance
- To enhance bioavailability
- To overcome first pass metabolism

Review of literature

- **Mizumoto *et al* *(2005)*[26]** developed novel fast disintegrating tablets of acetaminophen by direct compression method using saccharides. Saccharides are divided into high/low compressible categories to improve particle modification by coating and granulating low compressibility saccharide with high one, enable the production of fast disintegrating tablet.
- **Fukami J *et al* (2006)[27]** have formulated rapidly disintegration tablet of ethenzamide using a glycine as a disintegrant. Wetting time prepared from carboxymethyl cellulose having the hardness of 4 kg/cm^2 was 3 sec. Tablet containing croscarmellose showed fastest disintegration compared to other formulations. Ethenzamide did not affect the disintegration property, however, ascorbic acid prolonged disintegration time. It was suggested that the tablet formulation containing croscarmellose and glycine was highly applicable to water insoluble drug, such as ethenzamide.
- **Ahmed IS *et al* (2006)[28]** developed ketoprofen tablets which dissolve rapidly in the mouth. The solubility and dissolution rate of poorly water-soluble ketoprofen was improved by preparing a lyophilized tablet of ketoprofen using freeze-drying technique.
- **Avachat A *et al* (2007)[29]** have worked on the characterization and evaluation of spray dried co-processed excipients and their application in solid dosage forms. The work, which evaluates and characterizes two spray dried co-processed materials, one comprising of microcrystalline cellulose, colloidal silicon dioxide and sodium starch glycolate and other composed of microcrystalline cellulose, colloidal silicon dioxide and crospovidone. This study revealed that, the co-processed materials have excellent flow properties, high compressibility, render low disintegration time to tablets and have better binding properties.
- **Gohel MC *et al* (2007)[30]** have prepared a novel co-processed disintegrants consisting of crospovidone and sodium starch glycolate, to assess the efficacy of co-processed disintegrants. Cefixime trihydrate and ibuprofen tablets containing co-processed disintegrants exhibited quick disintegration and improved drug dissolution.
- **Furtado S *et al* (2008)[31]** prepared orodispersible tablets of famotidine using camphor as subliming agent and sodium starch glycollate together with crosscarmellose sodium as superdisintegrants. The formulations were evaluated for weight variation, hardness and friability, drug content, wetting time, *in vitro* and *in vivo* dispersion time, mouth feel and *in vitro* dissolution. The results revealed that the tablets containing subliming agent had a good dissolution profile.
- **Yoshio *et al* (2008)[32]** evaluated the effect of lubricant on the characteristics of orally disintegrating tablets using the phase transition of sugar alcohol. Mouth dissolving tablets were prepared by direct compression method using lactose-xylitol granules, disintegrants, glidant and lubricant with subsequent heating.
- **Chakraborty S *et al* (2008)[33]** have studied the comparative study on effect of natural and synthetic superdisintegrants in the formulation of fast dissolving tablets. The effect of natural superdisintegrants like isolated mucilage of plantago ovata and synthetic superdisintegrant like sodium starch glycolate and croscarmellose sodium were compared in the formulation of fast dissolving tablet. Fast dissolving tablet of aceclofenac were prepared by direct compression method. The formulation AM4 shows the highest swelling index and disintegration time of 13 sec. and drug release 98.76% within 30 minute.
- **Jacob *et al* (2009)[34]** prepared a microencapsulated fast melt tablets of ambroxol

hydrochloride using natural polysaccharide, pectin to mask the bitter taste. The microspheres were prepared by solvent evaporation method and tablets were prepared by melt granulation technique and resulting granules were showed fast melt at body temperature.

PAST WORK ON ERGOTAMINE TARTRATE

- **Dalia FET *et al* (2014)**[58] Prepared the insert by applying freeze drying technique using 2% w/w of different polymers. The prepared inserts were evaluated for appearance, bioadhesion potential, water uptake, in vitro drug release and imaged by scanning electron microscopy. The results showed that the prepared nasal inserts have a smooth surface and a spongy-like appearance. No interaction occurred between the drug and different polymers as revealed in DSC and FT-IR. Higher viscosity of the polymer causes a greater degree of water uptake and high bioadhesion potential; this in turn reduces the drug release, as the diffusional path length of drug becomes longer. The study revealed an inverse relationship between water uptake, bioadhesion potential and in vitro drug release. The order of drug release from different inserts is HPMC E5 > PVP K90 > Sodium aliginate > Carrageenan > NaCMC > Xanthan Gum > Chitosan.
- **Dileep Bhosale *et al* (2014)**[59] Developed a novel, simple and rapid, stability-indicating reversed-phase HPLC method and subsequently validated for simultaneous estimation of prochlorperazine maleate (PCM), ergotamine tartrate (EGT), paracetamol (PCL) and caffeine monohydrate (CFN) in tablet dosage form. The separation was achieved in 18 min on Purospher star RP-18e (150×4.6) mm, 5 µm column in gradient mode with flow rate 1.0 ml/min. Mobile phase A was 0.4% octane sulphonic acid sodium salt in water: glacia acetic acid (100:0.4) v/v and Mobile phase B was acetonitrile. Detection of all components carried out at 255 nm using a photodiodearray detector. The retention times of paracetamol, caffeine monohydrate, ergotamine tartrate and prochlorperazine maleate was found 3.5, 5, 10.5 and 15.5 min respectively. Specificity was established on combination drug product by hydrolytic and oxidative stress conditions. Validation of analytical method was carried out as per the current ICH guidelines for linearity, recovery, precisionlimit of detection, limit of quantification and robustness parameters.
- **Anna J (1999)**[60] Has applied High Performance Liquid Chromatography to determine Cyclizine Hcl, Caffeine and Ergotamine Tartrate in tablets. The chromatographic systems and the detection wavelengths were selected. The relationship between drug concentrations and peaks area, the accuracy and precision were tested by using the reference model mixtures.

Materials and Methodology

Plan of the research work:

➢ **Preformulation Studies:**

- Selection of excipients and its combinations suitable for the fast dissolving drug delivery system.
- Drug-excipients compatibility study.
- Preparation of standard calibration curve of Ergotamine Tartrate in ethanol and phosphate buffer pH 6.8.

➢ **Design of FDT Formulations of Ergotamine Tartrate by Direct Compression Method**

Table-1: Materials Used

Sl. No.	Materials	Source
1.	Ergotamine Tartrate	*Inga LAB Ltd, Mumbai, Maharastra.*
2.	Crospovidone	Gift sample from Wockhardt Research Centre, Aurangabad.
3.	Croscarmellose sodium	Gift sample from Wockhardt Research Centre., Aurangabad.
4.	Mannitol (Pearlitol SD 200)	Strides Arco Labs, Bangalore.
5.	Microcrystalline cellulose (PH 102)	Alkem Labs Pvt. Ltd., Mumbai.
6.	Mg. stearate	Sd Fine Chemicals, Mumbai.
7.	Talc	Sd Fine Chemicals, Mumbai.
8.	Orange flavor	Alkem Labs Pvt. Ltd., Mumbai.
9.	Potassium dihydrogen orthophosphate	Sd Fine Chem Limited, Mumbai.
10.	Ethanol	Qualigens Fine chemicals, Mumbai.

Drug Profile:

Ergotamine Tartrate

Ergotamine tartrate is a vasoconstrictor and alpha adrenoreceptor antagonist. Thus it is primarily used to treat migraine.

Class: Anti-Migraine.

Structural formula:

- Chemical name: : (5′α)-12′-Hydroxy–2′-methyl-(phenylmethyl)ergotaman–3′,6′,18–trione
- Proprietary names : Enxak; Ergodryl Mono; Ergokapton; Ergomar; Ergostate Ergotan; Gynergen(e); Lingraine; Migrexa. It is an ingredient of Cafergot and Migril.
- Molecular formula: (C33H35N5O5)2,C4H6O6
- Molecular weight: 581.6615 g/mol.
- Description: A white or almost white crystals or crystalline powder.

Physicochemical Properties:

- Solubility (mg/ml): Soluble 1 in about 500 of water and 1 in 500 of ethanol; practically insoluble in chloroform and ether.
- Melting point: 212° to 214°.
- Storage: Store at controlled room temperature (59 to 86 F), protect from heat and sunlight.

Mode of Action:

It acts on migraine by one of two proposed mechanisms;

1. It appears to bind to dopamine D2 receptors where it is a receptor antagonist. And is also a mixed 5-HT4 receptor agonist.
2. The anti-emetic action of metoclopramide is due to its antagonist activity at D2 receptors in the chemoreceptor trigger zone(CTZ) in the central nervous system(CNS).

Pharmacokinetics:

- Bioavailability: Oral:<1% (Enhanced by co-administration of caffeine)
- Half-life: 2 hr
- Plasma protein binding: Not available
- Excretion: 90% biliary.

Drug Interaction:

- Co administrataion of Ergotamine with potent CYP inhibitor has been associated with acut ergot toxicity, characterised by vasospasm and ischemia of the extremities.
- Cerebral ischemia in patients on protease inhibitor therpy when ergotamine was co administered.

Adverse reaction:

- Cardiovascular- Vasoconstrictive complication of a serious nature may occur at times. These include ischemia, cyanosis, absence of pulse, cold extremities, gangrene, precordial distress and pain. Other includes tachycardia or bradycardia and hypertension.
- Gastrointestinal- Nausea and vominting.
- Neurological- Paresthesia, numbness,weakness and vertigo.
- Allergic-Localized edema and itching.
- Fibrotic complication - there have been rare reports of fibrotic thickening of aortic, mitral, tricuspid.
- Drug abuse and dependence- Long term use of Ergotamine tartrate should be avoided.
- Dose: Not more than 8 mg of ergotamine tartrate in a day or 12 mg in any one week.

Excipients ;

Crospovidone (cp) ,Croscarmellose sodium (ccs) ,Magnesium stearate ,Talc ,Mannitol And Microcrystalline cellulose .

Formulation Of Fast Dissolving Tablets

Direct Compression Method: [66]

Fast dissolving tablets of Ergotamine tartrate were prepared by direct compression method, using synthetic superdisintegrants crospovidone and croscarmellose sodium in different ratios and directly compressible MCC (PH-102) as diluent and mannitol to enhance the mouth feel. According to the formulae given in Table-4 and 5,

- All the ingredients were passed through #60 mesh separately.
- The drug and MCC (PH-102) were mixed by small portion of both each time and blending it to get a uniform mixture and kept aside.
- Then the ingredients were weighed and mixed in geometrical order. And the mixed blend of excipients was compressed using 8 mm flat bevel edged punches to get a tablet of 200 mg weight in a (Clit pilot press 10 station compression machine).

Table-2: Formulation table for Ergotamine tartrate Fast Dissolving Tablets (1 tablet)

Ingredients (mg/tablet)	Formulation Code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug	4	4	4	4	4	4	4	4	4	4
Crospovidone	25	50	75	100	125	--	--	--	--	--
CCS	--	--	--	--	--	25	50	75	100	125
Magnesium stearate	2	2	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3	3
Mannitol	10	10	10	10	10	10	10	10	10	10
Orange flavour	2	2	2	2	2	2	2	2	2	2
MCC (PH-102)	154	129	104	79	54	154	129	104	79	54
Total weight	200	200	200	200	200	200	200	200	200	200

Drug- Ergatamine tartrate; CCS- Croscarmellose Sodium

Table-3: Formulation table for Ergotamine tartrate Fast Dissolving Tablets (50 tablets)

Ingredients (mg/50tablet)	Formulation Code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Drug	200	200	200	200	200	200	200	200	200	200
Crospovidone	1250	2500	3750	5000	6250	--	--	--	--	--
CCS	--	--	--	--	--	1250	2500	3750	5000	6250
Magnesium stearate	100	100	100	100	100	100	100	100	100	100
Talc	150	150	150	150	150	150	150	150	150	150
Mannitol	500	500	500	500	500	500	500	500	500	500
Orange flavour	100	100	100	100	100	100	100	100	100	100
MCC (PH-102)	7700	6450	5200	3950	2700	7700	6450	5200	3950	2700
Total weight	10000	10000	10000	10000	10000	10000	10000	10000	10000	10000

Drug- Ergatamine tartrate; CCS- Croscarmellose Sodium

Results

Table-4: Standard Graph of Ergotamine Tartrate in Ethanol (λ_{max} 314nm)

Sl. No.	Concentration (mcg/ml)	Absorbance			
		I	II	III	Mean ± SD
1.	0	0.000	0.000	0.000	**0.000±0.000**
2.	3	0.095	0.111	0.102	**0.103±0.006**
3.	6	0.169	0.178	0.181	**0.176±0.010**
4.	9	0.280	0.261	0.270	**0.270±0.009**
5.	12	0.350	0.368	0.361	**0.360±0.009**
6.	**15**	**0.486**	**0.497**	**0.481**	**0.488±0.008**

$a = 0.003$; $b = 0.031$; $r^2 = 0.994$

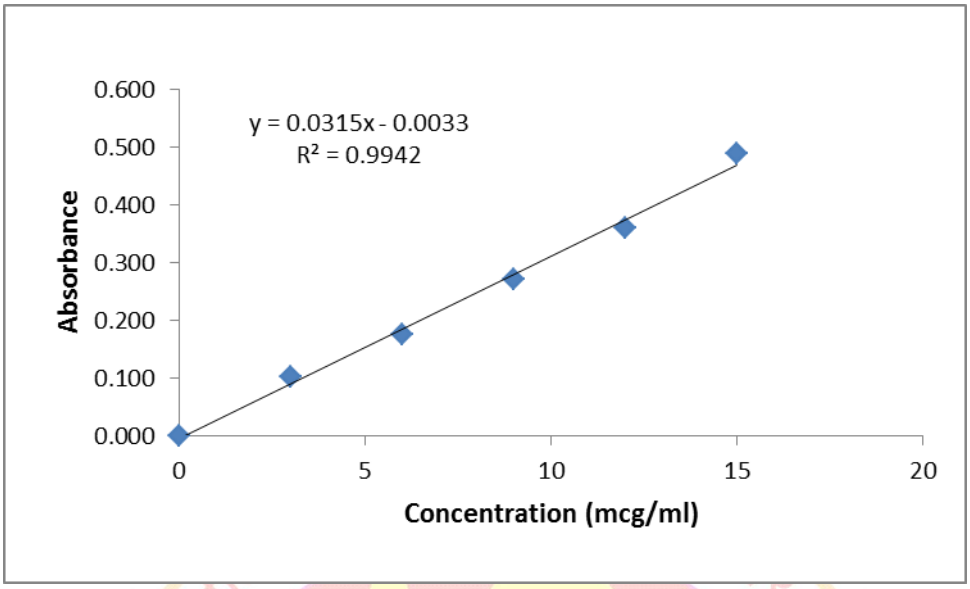


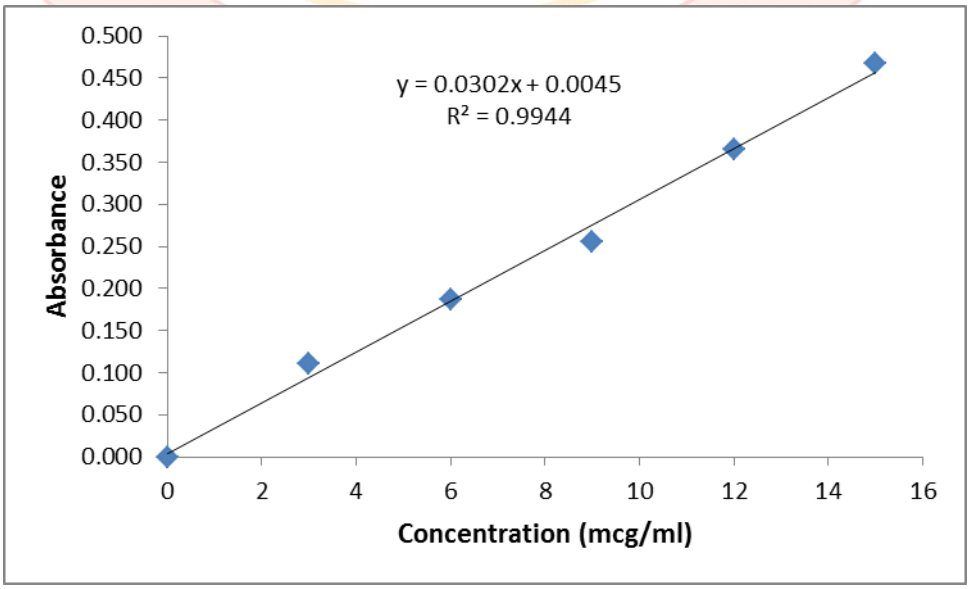
Figure showing Standard Graph of Ergotamine Tartrate in Ethanol (λ_{max} 314nm)

Table-4: Standard Graph of Ergotamine Tartrate in pH 6.8 Phosphate Buffer (λ_{max} 316nm)

Sl. No.	Concentration (mcg/ml)	Absorbance			
		I	II	III	Mean ± SD
1.	0	0.000	0.000	0.000	0.000±0.000
2.	3	0.104	0.116	0.113	0.111±0.009
3.	6	0.183	0.196	0.180	0.186±0.012
4.	9	0.267	0.243	0.257	0.256±0.012
5.	12	0.368	0.356	0.371	0.365±0.008
6.	15	0.468	0.479	0.456	0.468±0.012

Chart Area

a= – 0.004; b= 0.030; r^2= 0.994



Standard Graph of Ergotamine Tartrate in pH 6.8 Phosphate Buffer (λ_{max} 316 nm)

Table-5: Pre-compression Parameters of Formulations Prepared by Direct Compression Method

SI. No.	Formulation code	Angle of Repose (θ)	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Carr's Index (%)	Hausner's Ratio
1.	F1	27.49	0.55	0.69	20.29	1.25
2.	F2	30.13	0.48	0.59	18.64	1.23
3.	F3	29.1	0.45	0.54	16.67	1.20
4.	F4	30.22	0.47	0.58	18.97	1.23
5.	F5	27.86	0.50	0.63	20.63	1.26
6.	F6	29.57	0.48	0.62	17.74	1.22
7.	F7	30.67	0.57	0.65	12.31	1.14
8.	F8	29.31	0.49	0.58	15.52	1.18
9.	F9	28.43	0.56	0.66	15.15	1.18
10.	F10	28.94	0.53	0.63	15.79	1.19

Table-6: Post-compression Parameters of Formulations Prepared by Direct Compression Method

Parameters	Formulation code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Hardness*±SD (kg/cm²)	3.07± 0.15	3.40± 0.26	3.23± 0.28	3.53± 0.35	3.17± 0.40	3.27 ± 0.15	3.40 ± 0.10	3.37 ± 0.21	3.10 ± 0.44	3.57 ± 0.15
Thickness*±SD (mm)	2.13± 0.15	2.10± 0.10	2.10± 0.00	2.13± 0.06	2.17± 0.06	2.10±0.1 0	2.03± 0.06	2.13± 0.15	2.20± 0.10	2.03± 0.06
Friability (%)	0.85	0.61	0.76	0.55	0.96	0.50	0.70	0.45	0.80	0.85
In-vitro disintegration time*± SD (Sec)	47.67± 1.53	34.00± 3.61	20.33± 1.53	14.33± 1.53	9.33± 1.15	73.67± 1.53	61.33± 2.08	42.67± 3.51	32.33± 2.08	17.33±1. 53
Wetting Time*± SD (Sec)	23.33± 1.53	18.33± 2.59	16.00± 1.00	12.33± 0.58	9.67± 0.58	32.67± 0.58	27.00± 1.73	26.33± 2.08	20.00± 2.00	12.33±2. 08
Water Absorption ratio*± SD (%)	74.47± 1.03	62.21± 1.74	83.87± 0.93	63.66± 1.09	60.48± 0.93	51.60± 0.17	73.40± 2.82	65.05± 1.36	85.58± 2.02	70.54±2. 07
Percent Drug Content*± SD	99.78± 0.05	98.76± 0.10	99.97± 0.11	101.40 ±0.04	99.55± 0.27	99.68 ± 0.07	100.76 ± 0.05	99.59 ± 0.12	101.68 ± 0.15	98.86 ± 0.43
Weight Variation (%)	(188.6-204.7mg) Within the IP limits of ± 7.5%									

Discussion

In the present study an attempt has been made to design and evaluate fast dissolving tablets of Ergotamine Tartrate by direct compression method.

Fast dissolving tablets of Ergotamine Tartrate were prepared by direct compression method using crospovidone and croscarmellose sodium as superdisintegrants in different ratios using directly compressible MCC (PH-102) as a diluent and mannnitol to enhance the mouth feel. The prepared formulations were evaluated for different biological, physical and mechanical parameters.

According to the plan of work, the tablets were evaluated for their appearance, thickness, hardness, friability, weight variation, *in vitro* disintegration time, wetting time, water absorption ratio, drug content, *in vitro* release, short-term stability and drug excipient interaction.

The appearance of prepared tablets was smooth and uniform on physical examination. The hardness of the tablet formulations made by the direct compression method were found to be in the range of 3.07±0.15 to 3.57±0.15 kg/cm², indicating good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling (Table-13).

The weights of all the tablets were found to be uniform with low values of standard deviation and

within the prescribed IP limits. The thicknes and weight of the prepared fast dissolving tablets were found to be in the range of 2.03±0.06 to 2.20±0.10 mm and 188.6 to 204.7 mg respectively.

Conclusion

In the present work, fast dissolving tablets of Ergotamine Tartrate were prepared by direct compression method.

Fast dissolving tablets of Ergotamine Tartrate were prepared by direct compression method using synthetic superdisintegrants such as crospovidone and croscarmellose sodium in different ratios using directly compressible MCC (PH-102) as a diluents and mannitol to enhance the mouth feel and evaluated for different biological, physical and mechanical parameters.

All the tablets of Ergotamine Tartrate were evaluated for their appearance, thickness, hardness, friability, weight variation, *in vitro* disintegration time, wetting time, water absorption ratio, drug content, *in vitro* release, short-term stability and drug excipient interaction.

Based on the Above Studies, Following Conclusions were drawn:

- Tablets prepared by direct compression method were found to be good without any chipping, capping and sticking.
- The hardness of the prepared tablets were found to be in the range of 2.93 to 3.63 kg/cm²for direct compression method.
- The friability values of the prepared batches of tablets were found to be less than 1%.
- The low values of standard deviation for average weight and drug content of the prepared tablets indicate weight and drug content uniformity within the batches prepared.

Summary

Ergotamine tartrate is a vasoconstrictor and alpha adrenoreceptor antagonist. It is a anti-migraine, thus primarily used to treat migraine.

FDT will avoid missing out of a dose even during travelling or other situations, where there is no access to water. The concept of formulating fast disintegrating tablets containing Ergotamine tartrate offers a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with increased bioavailability.

In the present study, an attempt has been made to design and evaluate fast dissolving tablets of Ergotamine tartrate using crospovidone and croscarmellose sodium synthetic superdisintegrants in different ratios using directly compressible MCC (PH-102) as a diluent and mannitol to enhance the mouth feel.

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