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Preparation and characterization of oral fast dissolving film of hydralazine HCL

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Abstract

Hydralazineis a BCS class III antihypertensive drug. The main aim of this study is to improve the dissolution and thus the bio availability of hydralazine by preparing fast dissolving oral films of Hydralazine HCl. The objective of this study is to enhance therapeutic efficacy, compliance & convenience of geriatric and pediatric patients by preparing hydralazine fast dissolving oral films by solvent casting method. The hydralazine films were prepared by using different film forming polymers. Various grades and concentrations of hydroxypropyl methylcellulose (HPMC) E 3 and E 15, methyl cellulose (MC), sodium carboxy methyl cellulose (CMC), varying the surfactants like Sodium Lauryl Sulfate (SLS) and Poly vinyl pyrrolidone (PVP) are used. Morphological studies, Thickness uniformity, Folding endurance, Drug content uniformity test, In vitro dissolution studies, Weight variation tests were performed for evaluation of films.The film formulation F12 having HPMC E 15, PVP and Glycerol showing the greatest dissolution and bio availability and could give quick onset of action upon administration when compared to other formulations.

Keywords: Hydralazine Hcl, oral fast dissolving films, hydroxypropyl methylcellulose, sodium carboxy methyl cellulose, solvent casting method.

Introduction

Hydralazine is a BCS class III anti hypertensive drug. It is a hydralazine derivative vasodilator used in the treatment of diseases like hypertension and heart failure. It interferes with calcium transport may be by preventing influx and efflux of calcium into cells, resulting that to relax arteriolar smooth muscle and lowers the pressure of blood. This results in decreased vascular resistance leads to increased heart rate, stroke volume, and cardiac output(1-3). Among all the drug delivery routes, the oral route is the most preferred route due to its ease of administration, non-invasiveness, adaptability, patient compliance and acceptability (4).Oral Solid dosage forms also have impervious difficulties in patients especially for geriatric and pediatric patients. Dysphasia is most common among all age group patients(5). Research and development in the oral drug delivery systems has led to transition of dosage forms from simple conventional tablets/capsules to modified release tablets or capsules to oral disintegrating tablet (ODT) to wafer to oral Dissolving Films. Many pharmaceutical firms have directed their research activity in reformulating existing drugs into new dosage forms like films. Fast dissolving oral films constitute an innovative dosage form that overcome the swallowing problem and provides speedy onset of action.

A fast-dissolving oral film drug delivery system is a film containing active pharmaceutical ingredient and hydrophilic polymers that rapidly dissolves or disintegrates in the saliva, with an in-vitro disintegration time of approximately 30 seconds without the need of water or chewing(6).

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Basically the FDOFs can be considered as an ultra-thin postage stamp size strip contains active pharmaceutical ingredient and other excipients. The introduction of FDOFs in market was accompanied by educating the mass about the proper way to administer the product like giving instructions “do not swallow” or “do not chew”In this present study, the hydralazine Hcl oral films were prepared by solvent casting technique. The main advantages of this technique are greater uniformity of thickness, Greater film clarity, more flexibility, and better physical properties than other methods like hot melt and solid dispersion extrusion methods(7).

Materials and Methodology

Materials

In this present study, the hydralazine Hcl films were prepared by solvent casting technique. hydralazine hcl was purchased from aurobindo pharma and bio adhesive hydrophilic polymers like Hydroxyl propyl methyl cellulose (HPMC) E 3 and E 15was purchased from Loba chemic pvt. Ltd, Mumbai, Yarrow chem products, methyl cellulose (MC), sodium carboxy methyl cellulose (CMC) from Merck specialitiespvt.Ltd, varying the surfactants like Sodium Lauryl Sulfate (SLS), Poly vinyl pyrrolidone(PVP) and other ingredients like SLS, PVP, Citric acid, mannitol, flavouring , colouring agents and distilled water were used in the formulation of films.

Methods

***Preformulation Studies*:** These studies may be described as a stage of development during which the physicochemical and biotherapeutical properties of a drug substance are characterized. It is an essential step in the drug development. Pre-formulation studies are an investigation of physical and chemical properties of the drug substances alone and combined with excipients like colour, form, melting point, and solubility studies, micrometric properties, compatibility studies, analytical studies etc. The information produced during this phase is used for making critical decisions in subsequent stages of development.(8)

The API was Tested for the Following Properties

- Organoleptic Properties
- Melting point
- Solubility
- Drug – Excipients compatibility studies

***Organoleptic Properties*:** The drug sample was viewed under the compound microscope for the determination of drug morphology by using the black and white backgrounds. Then the results were compared with the official books and United States Pharmacopoeia.

***Melting Point*:** Melting point of hydralazine was determined by using melting point apparatus.

***Solubility*:** According to the Indian Pharmacopoeia the drug solubility was studied in different solvents (aqueous and organic).The drug solubility was checked in methanol, PEG, water. The drug shows maximum solubility in methanol and it is partially soluble in water.

Calibration Curve of Hydralazine HCL in Artificial Saliva Buffer

***Preparation of Artificial Saliva Buffer*:** 0.844 gm of Nacl,1.2 gm of Kcl, 0.93 gm of $Cacl_{2,}$ 0.11 gm of Mgcl,0.342 gm of KPO_4 were weighed and added one by one to 500 ml of distilled water and then the volume was made up to 1000 ml by using water then the pH was adjusted to PH 5.8 with 0.1N hydrochloric acid.(9)

***Preparation of Stock Solution*:** 10mg of HYDRALAZINE HCL was dissolved in 10ml of pH 5.8 Artificial saliva buffer (1000µg/ml). 1ml of this solution was taken in 100 ml volumetric flask, and made up to volume with pH 5.8 Artificial saliva buffer.

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***Preparation of Standard Solution*:** The above solution was subsequently diluted with pH 5.8 Artificial saliva buffer to obtain series of dilutions containing 10, 12, 14, 16, 18, 20 µg/ml of HYDRALAZINE HCL. The absorbance of the above dilutions was measured at 235nm by using UV- Spectrophotometer taking pH 5.8 artificial saliva buffer as blank. Then a graph was plotted by taking concentration on X-axis and absorbance on Y-axis which gives a straight line.

Manufacturing Methods

Preparation of Hydralazine Oral Fast Dissolving Films by Solvent Casting Method

- Oral dissolving films are formulated by using the solvent casting method, Drug (HydralazineHcl) was dissolved in sufficient amount of methanol.
- Then the polymers (HPMC E 3, E 15) were completely dissolved in suitable amount of hot water.
- Other ingredients like SLS, PVP, Citric acid, mannitol, flavouring and colouring agents are added one by one in a test tube containing distilled water.
- These three solutions were mixed vigorously and finally this solution was casted on a Petri dish and dried in hot air oven at 50°C for 4 hours. The films were carefully removed from Petri dish, checked for any imperfections. The samples were stored in the desiccators for further analysis(10)
- The Formulation of HYDRALAZINE HCL Oral Fast Dissolving Films was given in Table 1.

Evaluation Oral Fast Dissolving Films

- Morphological studies
- Thickness uniformity
- Folding endurance
- Drug content uniformity test
- Invitro dissolution studies
- Weight variation
- Disintegration time

***Morphological Studies*:** A visual inspection for physical appearance of films and evaluation of texture was done by feel and touch(11)

***Thickness Uniformity*:** All the batches were evaluated for thickness by using calibrated vernier calipers with a least count of 0.01mm. The film was placed in between anvil and pressor foot of thickness gauge and the reading on the dial was noted down. The thickness was measured at different spots of three randomly selected films of each formulation. Calculate the average thickness of film. Uniform thickness of film is essential as it is directly related to accuracy of dose distribution in the film(12). The results were given the Table 2.

***Folding Endurance*:** Folding endurance is a procedure to estimate the mechanical properties of a film and it also gives an indication of brittleness of film. The folding endurance was measured manually for the prepared films to determine the flexibility of films. A strip of film of specific size (1*1 cm) was cut and repeatedly folded at the same place till it breaks. The film was folded at the same place until the film breaks(13). The results were given the Table 2.

***Drug Content Uniformity Test*:** One cm^2 film was taken in a 100 ml volumetric flask and dissolved in 5 ml of artificial saliva buffer and then final volume was made up with artificial saliva buffer. Samples were suitably diluted with artificial saliva and the absorbance was measured at 228 nm (14). The results were given the Table 2.

***Disintegration Time*:** Disintegration time of film is the time required by oral film to start breaking when brought in contact with water or saliva. The disintegration time depends upon the composition of the films. Generally, it ranges from 5-30 seconds. There are no official guidelines to determine the disintegration time of oral films. One of the methods is dipping the film in 25 ml water or saliva in a beaker. The beaker should be

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shaken gently and the disintegration time was noted(15). The results were given the Table 2.

In Vitro Dissolution Studies

Take 500 ml of artificial saliva solution as dissolution medium to perform in vitro dissolution studies in modified type 5 dissolution apparatus. A temperature of 37°C and 25 rpm was used. Each film with a dimension of appropriate size equivalent to 30 mg of HydralazineHClwas placed on a watch glass covered with nylon wire mesh. The watch glass was then dropped into a dissolution flask. 5 ml samples were withdrawn at 1,2,3,4,5,10, 20, 30 min time intervals and every time replaced with 5 ml of fresh dissolution medium. The samples were analyzed by measuring absorbance at 228 nm (16).

Results and Discussion

Active Pharmaceutical Ingredient (API) Characterization:

***Oraganoleptic Evaluation*:** These are preliminary studies of any drug substance which is useful in identification of specific material. Following physico-chemical properties of API were studied. White powder having melting point 210-220 ^{O}C and Freely soluble in water and methanol (17).

***Calibration Curve of Hydralazine HCl in pH 5.8 Artificial Saliva Buffer by using UV - Visible Spectrophotometer*:** The calibration was used to determine the amount of HydralazineHCl in unknown solution. The series of dilutions containing 10, 12, 14, 16, 18, 20 µg/ml of Hydralazine HCl were analyzed at

Table 1. Formulation of Hydralazine HCl Oral Fast Dissolving Films

Compound	F1 (HPMC E3)	F2 (HPMC E5)	F3 (HPMC E15)	F4 (HPMC E3)	F5 (HPMC E 5)	F6 (HPMC E15)	F7 (HPMC E3)	F8 (HPMC E5)	F9 HPMC E3)	F10 (HPMC E3)	F11 (HPMC E5)	F12 (HPMC E15)
Drug (mg)	25	25	25	25	25	25	25	25	25	25	25	25
Methanol (gm)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Polymer (mg)	300	300	300	300	300	300	300	300	300	300	300	300
(SLS) (mg)	–	–	–	25	25	25	2	2	2	–	–	–
(PVP) (mg)	2	2	2	–	–	–	–	–	–	2	2	2
PEG (mg)	25	25	25	25	25	25	-	-	-	-	-	-
Glycerol (mg)	–	–	–	–	–	–	25	25	25	25	25	25
Water (gm)	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7
Total	4552	4552	4552	4575	4575	4575	4552	4552	4552	4552	4552	4552

Hydralazine HCL

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Table 2. Results of OFDFs of Hydralazine HCl Containing Evaluating Parameters as Drug Content, Weight Variation, Thickness Uniformity, Disintegrating Time, Folding Endurance

Formulation	Evaluation Parameters				
	Drug Content (1*1 cm)(mg)	Weight Variation (gm)	Thickness Uniformity (µm)	Disintegration Time (sec)	Folding Endurance
F1	15.0	0.21±0.01414	56.5±0.70711	5 sec	120
F2	9.3	0.15±0.0070	50.5±0.70711	3.1 sec	125
F3	6.4	0.19±0.01414	54±1.41421	2.2 sec	115
F4	19.2	0.13±±0.02828	52.2±0.70711	5.1 sec	95
F5	19.3	0.25±0.021213	51.5±0.70711	6.2 sec	123
F6	13.3	0.26±0.01414	56.1±2.0506	1.2 sec	122
F7	8.9	0.26±0.01414	53.5±2.969	5 sec	58
F8	15.9	0.28±0.007071	56±1.41421	2.5 sec	140
F9	6.1	0.275±0.042426	59.5±0.70711	12 sec	99
F10	15.8	0.16±0.02828	57±1.41421	1.6 sec	85
F11	18.1	0.26±0.01414	53±2.820	3.5 sec	125
F12	19.5	0.285±0.0212	51±1.41421	2.9 sec	130

absorbance of 235 nm. The absorbance values of the various concentrations of Hydralazine Hclpure drug in pH 5.8 Artificial saliva were checked. Calibration curve of Hydralazine Hcl in pH 5.8 artificial saliva buffer was plotted between the absorbance and concentration of the HydralazineHCl. The correlation coefficient (r^2) value is about 0.994indicates that the hydralazine follows Beer's Lamberts Law.

Analytical Methods

***Spectrophotometric Method*:** A number of methods are reported in the literature for the Estimation of Hydralazine HCL (IP). By using pH 5.8 artificial saliva buffer as a dissolution medium to calibrate Hydralazine HCL drug.

***In Vitro Dissolution Studies*:**

Take 500 ml of artificial saliva solution as dissolution medium to perform in vitro dissolution studies in modified type 5 dissolution apparatus. A temperature of 37°C and 25 rpm was used. Each film with a dimension of appropriate size equivalent to 30 mg of HydralazineHClwas placed on a watch glass covered with nylon wire mesh. The watch glass was then dropped into a dissolution flask. 5 ml samples were withdrawn at 1,2,3,4,5,10, 20, 30 min time intervals and every time replaced with 5 ml of fresh dissolution medium. The samples were analyzed by measuring absorbance at 228 nm (16).

Analytical Methods

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Evaluation Oral Fast Dissolving Films:

***Morphological Characters*:** Prepared Hydralazine HCl fast dissolving films were transparent and colorless, all the films were smooth in texture and glossy in appearance.The results were shown in (Table 2).

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***Drug Content Uniformity Test*:** Films of 1*1 cm were cut from different regions and the drug content in the films was evaluated and the values were found in between 6 to 20 mg. The results were shown in (Table 2).

***Weight Variation*:** The film was cut from different regions and the weight variation was determined and the values were found in between 0.24 to 0.27 g.The results were shown in (Table 2).

***Thickness Uniformity*:** The thickness was measured at 3 different regions of film by using vernier calipers and the values were found in between 50 to 60 µm.The results were shown in (Table 2).

***Disintegration Time*:** The film was cut in to 1*1 mm and placed it in petri dish, now add a drop of water at the center of the film measure the time taken to disintegrate and noted. In the same manner repeat it same with the buffer. The disintegration time values were found in between 1.2 to 12 sec.The results were shown in (Table 2).

***Folding Endurance*:** The folding endurance was measured at different regions of film by repeated folding at 180^0 angle of the plane at the same place till the film breaks. The number of times the film was folded without breaking was computed as the folding endurance value. The folding endurance of films was measured at different regions and the values were found in between 96 to 147.The results were shown in (Table 2).

***Dissolution Rate Studies*:** The in-vitro dissolution studies were conducted using pH 5.8 buffer as dissolution medium. The percent of Hydralazine HCL dissolved at the various time intervals were calculated and plotted against time. The graphical plots of percentage of Hydralazine HCL dissolved versus time were placed in (Figure. 1).

The cumulative % of hydralazine released at the end of 5min is 98.87 for F12 formulation. Complete drug release from F12 is significantly higher i.e., about 98% of drug was released when compared to other formulations.

In f12 formulation, HPMC E15, Glycerol, PVP were added to the formulation gave superior dissolution properties when compared to other formulations.

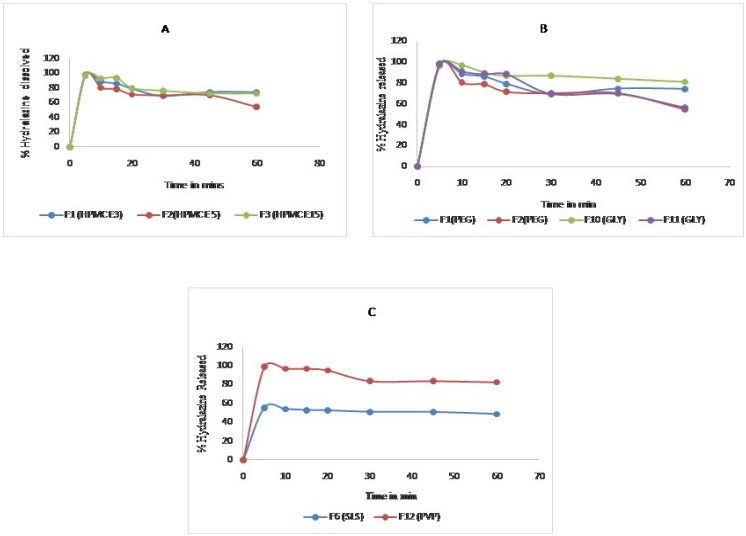

Fig 1. Comparative *In Vitro* Drug Release Profile of Hydralazine fromFilms A. Effect of Polymers B. HPMC E 15 with Plasticizers C. HPMC E 15 with Surfactants

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Conclusion

The current investigation established an effective and easy method to formulate hydralazine Hcl films to increase its water solubility and also its dissolution. OFDF were prepared by solvent casting method through OFDF proved to have the best results in terms of solubility and dissolution. The formulation F12 containing HPMC E 15 with glycerol and PVP gave superior dissolution properties when compared to other formulations. The rise in dissolution efficiency leads to improve bio availability. It would also facilitate quick onset of action after oral administration of films hence improving patient compliance. This can serve as a novel approach for the treatment of cardiovascular diseases.

References

1. Paul Saini, Anoopkumar. *(2012)* .Fast Disintegrating Oral Films: A Recent Trend of Drug Delivery, *International journal of Drug Development & Research.*

2. M.D. Nehal Siddiqui, Garima Garg and Pramod Kumar Sharma.(2011).A Short Review on “A Novel Approach in Oral Fast DissolvingDrug Delivery System and Their Patents.”Biological Research.

3. Reddy LH and Ghosh BR .(2002). Fast dissolving drugdelivery systems. A review of literature. *Indian J Pharm Sci.*

4. Suresh B, Halloran D and James L.(2012).Quick dissolving films: A novel approach to drugdelivery. *Drug Dev Tech.*

5. Apoorva Mahajan, Neha Chhabra, Geeta Aggarwal .(2011). Formulation and Characterization of FastDissolving Buccal Films. A Review.Scholars Research library.

6. Indian Pharmacopoeia – 1996, volume II.

7. Raymond craowe, Paul J. sheskey. “Hand Book of Pharmaceutical Excipients”.

8. Jayasravani B, Sai Kishore V, Lakshmana Rao R.(2014).Design and Development of Fast Dissolving Films of Diltiazem Hydrochloride. Inventi Rapid: Pharm Tech.

9. Vaishali Y. Londhe* and Kashmira B. Umalkar.(2012). “Formulation Development and Evaluation of Fast Dissolving Film of TelmisartanIndian J Pharm Sci.

10. Chen M, Tirol G, Schmitt R, Chien C and DualehA.(2006). “Film forming polymers in fast dissolve oral films”, *AAPS Annual meetings-posters and papers*.

11. K.Maheswari.(2014). “Development And Evaluation Of Mouth Dissolving Films Of Amlodipine Besylate For Enhanced Therapeutic Efficiency” Journal of Pharmaceutics.

12. Anoop Kumar. (2013). “HPMC/CMC Based Fast Dissolvable Oral Films of an Anxiolytic: In Vitro Drug Release and Texture Analysis” International Journal of Drug Delivery.

13. Amal S. M. Abu El-Enin.“Preparation And Evaluation Of Fast Dissolving Oral Films Containing Metoclopramide Hydrochloride, World Journal Of Pharmacy And Pharmaceutical Sciences.

14. Buchi N. Nalluri*, B. Sravani. (2013). “Development and Evaluation of Mouth Dissolving Films of Sumatriptan Succinate for Better Therapeutic Efficacy” Journal of Applied Pharmaceutical Science.

15. Ravi Garala.“Formulation And Evaluation Of Fast Dissolving Film Of Cyproheptadine Hydrochloride, International Journal Of Pharmaceutical Research.

16. Pratik Kumar, Joshi Harsha Patel.(2012). “Formulation Development And Evaluation Of Mouth Dissolving Film Of Domperidone, J Pharm Bioallied Sci.

17. Patel JG. (2012). “Formulation and Evaluation of Mouth Dissolving Film of Domperidone”, International Journal for Pharmaceutical Scholars (IJPRS), Researched Article.

18. Mashru RC, Sutariya VB, Sankalia MG and Parikh PP. (2005). “Development and

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10.5530/ctbp.2022.3s.75

evaluationof fast dissolving film of salbutamol sulphate". *Drug Dev Ind Pharm*.

19. M Koland, VP Sandeep, NR Charyulu. (2010). Fast Dissolving Sublingual Films of Ondansetron Hydrochloride: Effect of Additives on Invitro Drug Release and mucosal Permeation" Eur J Pharm Biopharm.

20. Ali S and Quadir A. (2007). "High molecular weight povidone based films for fast dissolving drug delivery applications". *Drug Del Tech*.

21. Pallavi Patil, S. K. Shrivastava. (2014). "Fast Dissolving Films: An Innovative Drug Delivery System"IJSR.