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FORMULATION DEVELOPMENT AND EVALUATION OF HYDRALAZINE MOUTH DISSOLVING TABLET

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ABSTRACT

Formulation and development of Mouth Dissolving Tablets (MDT) of Hydralazine that was dissolves or disintegrates within a minute in the oral cavity without the need of water and has a pleasant taste. Loading of hydralazine HCl on Tulsion 335 was carried out by batch process. Highest drug loading on resin was achieved when activated with both acid-alkali treatments. The absorption maxima of hydralazine HCl were observed at 220 nm. The thickness of the tablet was found 2.076 to 2.415 mm. The tablets with Crospovidone disintegrated faster than the tablets containing Ac-Di-Sol and sodium starch glycolate. The *in vitro* disintegration time of all the formulations varied between 20.66 ± 2.08 s to 66.33 ± 3.05 s. The in vitro wetting time of all the formulations varied between 18.66 ± 2.51 to 57.66 ± 3.51. *in-vitro* drug release experiments were performed at 37±0.5^{o}C in paddle type dissolution apparatus. The results showed that all the formulations release the drug within 6 to 7 minutes. The maximum drug release was found in formulation FDT2 (98.747%). The order of drug release was found to be: **FDT2 >FDT1 >FDT4 >FDT3 >FDT6 >FDT5.**

KEYWORD: Hydralazine, Mouth Dissolving Tablet, evaluation, superdisintigrant.

INTRODUCTION

Tablet dosage form is the most popular among all existing conventional dosage forms because of its convenience of self administration, compactness and easy manufacturing.[1,2,3] Mouth Dissolving Tablets MDT is a solid dosage form that dissolves or disintegrates within a minute in the oral cavity without the need of water and has a pleasant taste.[4,5] MDT is also known as orally disintegrating tablet, fast-dissolving tablet, fast-melting tablet, mouth melting tablet or fast-disintegrating tablet while European Pharmacopoeia adapted the term

'Orodispersible Tablets'.[6,7] Most benefits of MDT are for pediatric, geriatric and bedridden or developmentally disabled patients.[8,9] Patients with persistent nausea who are traveling or who have little or no access to water are also good candidates for MDTs.[10,11]

Hydralazine is a direct-acting smooth muscle relaxant used to treat hypertension by acting as a vasodilator primarily in arteries and arterioles.[12] Hydralazine is used to treat severe hypertension, but again, it is not a first-line therapy for essential hypertension.[13]

Development of a Hydralazine formulation would be a significant advantage for patient compliance accompanied by minimization of the drug side effects as a result of increase in heart rate, especially toxicity in long-term therapy.[14]

- To improve the pregnant patient compliance in hypertensive condition and during nausea.
- For those patients suffering from diarrhea and nausea during travel.
- To study the effect of combination and composition of various superdisintigrant in table.
- To study the effect of temperature and relative humidity on tablet characteristic.

MATERIAL AND METHODS

Hydralazine HCl was obtained from GlaxoSmithKline Pharmaceuticals Ltd., Mumbai, Ac-di- sol, Lactopress, Micro crystalline cellulose (MCC) and Sodium starch glycolate (SSG) from Qualigens fine chemicals, Navi Mumbai, Crospovidone from ACS chemicals, HPMC, Magnesium Stearate and Tulsion – 335 from Spectrochem Pvt. Ltd., Mumbai. All used solvents and chemicals were laboratory grade.

Drug characterization

Physical appearance: Physical appearance of drug was examined by organoleptic properties.
Melting point: Melting point of the Hydralazine was determined by Capillary fusion method; one sided closed capillary filled with drug and put into the Melting Point Apparatus. Temperature was noted at which solid drug converts into liquid.
Solubility: solubility of compound was determined by the dissolving the solute (drug) in the different solvents and solubility measured by UV- spectroscopy.

Estimation of the drug by Spectrophotometric method

Several methods are reported in the literature for the estimation of Hydralazine. In the present study, UV spectrophotometric method is selected for the estimation of Hydralazine.

Scanning for Ultraviolet Absorption Maxima (λmax)

Ultraviolet absorption in the rage 200 to 400 nm of a 10µg/ml solution in 0.1M HCl was measured. The absorption maximum (λmax) of hydralazine in this solution was found to be 220 nm which is concordant with the Clarke's Analysis.

FT-IR spectral analysis

Infra red spectroscopy is most powerful technique for qualitative compound identification. It gives information about the group present in the particular compound. The main application of FT-IR spectrophotometry is determination of the identity of a compound by means of spectral comparison with that of an authentic sample and verification of the presence of functional group in an unknown molecule. The IR analysis of the sample was carried out for qualitative compound identification. The pellet of approximately 01 mm diameter of the drug was prepared grinding 3-5 mg of sample with 100-150 mg of Potassium Bromide in pressure compression machine. The sample pellet was mounted in IR compartment and scanned at wavelength 4000 cm^{-1} – 500 cm^{-1}. On analysis of the IR spectra of in Clarke's Analysis pure drug major differences were observed in the absorption peaks pattern.

Preformulation study

Solubility

The solubility of hydralazine was determined in different solvent systems. Small amount of the drug was mixed with 4 ml of each solvent in screw capped glass tubes. The solutions were examined physically for the absence or presence of drug particles.

Preparation of calibration curve

Preparation of standard solutions

Hydralazine HCl 10mg was accurately weighed dissolved in 0.1N HCl and volume is makeup to 10 ml of 0.1N HCl to form a stock solution (1000µg/ml). 01 ml of the above solution was diluted upto 10ml with 0.1N HCl in a 10ml volumetric flask to give a concentration of 100µg/ml. The solution was filtered in a 0.45 µm membrane filter before the injection in the column.

Preparation of sample solutions

Aliquots of 1, 2, 3, 4 and 5 ml of working standard solution (100 mg/ml) was taken in a series of 10 ml volumetric flask and volume made up with 0.1N HCl, the final volumes prepared were 10, 20, 30, 40 and 50 µg/ml respectively. The absorbance measurements of these

solutions were carried out against water as blank at 220nm. A calibration curve of Hydralazine hydrochloride was plotted. The concentration of the unknown was read from the calibration graph or computed from the regression equation.

Drug polymer interaction studies

While designing mouth dissolving tablets, it was imperative to give consideration to the compatibility of drug and polymer used within the systems. It is therefore necessary to conform that drug is not interacting with polymer under experimental conditions (40±5 ^{O}C and 75±5% RH) for four weeks. Physical changes and absorption maxima were also evaluated at end of four weeks. The infrared absorption spectra of pure polymer and physical mixture of polymer and drug were run and between 4000 cm^{-1}-500 cm^{-1}.

Development of method of taste masking of hydralazine

Determination of threshold bitterness concentration of hydralazine

A panel of six healthy human volunteers (age 20-25) was selected. A series of solutions of hydralazine in 0.1 M hydrochloric acid of concentrations 10, 20, 30, 40, and 50 µg/ml were prepared. The volunteers hold 10 ml of each solution in oral cavity for 60s and rated the taste on a scale from 0 to 4 (0: no bitterness, 1: threshold bitterness, 2: bitter, 3: moderate bitterness and 4: strong bitterness). Rinsing the mouth by distilled water and a gap of 30 min were applied between successive tests. Based on the opinion of the volunteers, threshold bitterness concentration of hydralazine was judged.

Taste masking by formation of complexes with ion exchange resins; Activation of resin

Batch method was used to prepare drug resin complex. Ion exchange resins Tulsion-335 was swelled with deionised water for an hour and then washed with 1N hydrochloric acid and 1N sodium hydroxide in order to remove impurities (alkali and acidic impurities). The treated resin was washed several times with freshly prepared deionized water to remove the traces of acid or alkali. This treated resin was kept in oven for 12 h at 50^{0}C. The dried activated resin was kept in desiccator until in use.

Effect of various parameters on Drug-resin adsorption

Drug loading process was optimized for maximum drug loading considering parameters such as concentration of resin, stirring time, pH of resin solution on drug loading onto resin.

Effect of concentration of resin on drug loading

For optimizing drug: Resin ratio, Accurately weighed quantity of hydralazine (100 mg) was added to each of the four beakers containing 100, 200, 300 and 400 mg of Tulsion 335 swelled in 100 ml of deionized water. The mixture was stirred for an hour. Drug resin complex was collected by filtration, washed with 50 ml of deionized water and percentage of drug adsorbed onto each resin was determined.

Effect on swelling of ion exchange resin by stirring Speed and Time

To optimize the effect of swelling of ion exchange resin on drug loading, accurately weighed activated resin was stirred at 50 and 100 rpm for different time period (15, 30, 60 min) in 100 ml deionised water. After specified time, the drug (100 mg) was added, stirred for 4 h and filtered. It was then subjected to UV spectroscopy at 220 nm to determine the amount of drug loaded and then percentage of drug loaded was calculated.

Effect of complexation time on drug loading

To optimize the effect of complexation time on drug loading, accurately weighed hydralazine (100 mg) was added to 300 mg of tulsion 335 solution and slurred in 100 ml of deionized water in beaker. Five batches with stirring time of 1, 2, 3, 4, 5 h were processed for resin. The mixtures were filtered and subjected to UV spectroscopy at 220 nm to determine the amount of drug bound. Then percentage drug loading was calculated.

Effect of pH on drug loading

Hydralazine (100 mg) was added to Tulsion 335 (300 mg) in beaker containing 100 ml of different pH solutions. The pH was adjusted using standard solutions of hydrochloric acid and sodium hydroxide, stirred for 4 h. The mixtures were filtered and subjected to UV spectroscopy at 220 nm to determine the amount of drug complexed.

Optimizaton of formulation of drug resinate

Batch method was used to prepare drug-resin complex. The activated resin was swelled for 1 h in deionised water (300 ml) with homogenous continuous stirring on magnetic stirrer at 100 rpm. After swelling of activated resin (15 g), the hydralazine (5 g) was added to this solution and stirred on magnetic stirrer at 100 rpm for period of 4 h at pH 6.8. The obtained resinate was separated by vacuum filtration and dried in vacuum desiccator.

Preparation of non bitter Drug-resin granules

Drug was mixed with Tulsion 335 (1:3) with the help of glass mortar and pestle. Then 10% ethanol was added to mixture as granulating agent. The dump mass was converted into the granules by passing through sieve number 24. After granulation, they were dried at 50^0C in tray drier.

Evaluation of drug Resinate and Granules

***In- vivo* taste evaluation**

Taste evaluation of the drug resin complex was performed by panel of six healthy volunteers in the age groups of 25 to 30 years. The 5 mg equivalent to Hydralazine, Hydralazine resinate and Hydralazine granules were held in mouth for 60s by each volunteer, and the bitterness level was recorded using a numerical scale. After 60s, complex was spitted out and the mouth was rinsed thoroughly with mineral water.

Physicochemical evaluation

The various micromeritic properties of blend were tested given below:

Bulk density

Apparent bulk density (ρ_b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of powder (M) was determined. The bulk density was calculated using the formula:

$$\rho_b = \frac{M}{V_b}$$

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρ_t) was calculated using the formula:

$$\rho_t = \frac{M}{V_t}$$

Compressibility index

The simplest way for measurement of flow of powder is its compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (I) which is calculated as follows:

$$I = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

Where, ρ_t = Tapped density, ρ_b = Bulk density

Hausner ratio

Hausner ratio (HR) is an indirect index of ease of powder flow. It is calculated by the following formula:

$$HR = \frac{\rho t}{\rho b}$$

Where, ρ_t is tapped density and ρ_b is bulk density.

Lower Hausner ratio (< 1.25) indicates better flow properties than higher ones (> 1.25).

Angle of repose

Angle of Repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a specified cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose (θ) was calculated using the formula

$$\tan\theta = \frac{h}{r}; \text{ Therefore; } \theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Where, θ is Angle of Repose; h is height of cone; r is radius of cone

Determination of *in-vitro* drug release resinate

The release of drug from resinate was carried out from USP 24 dissolution apparatus II, paddle (USP 24, 2000). Three different dissolution media (900 mL) used were 50% ethanol, 0.1N HCl (pH 1.2) and Phospahte Buffer (pH 7.4) at 37±1^{0}C. Rotation speed was 50 rpm. An accurate weight of resinate equal to 5mg of hydralazine was added in dissolution media. Aliquots of 5ml was collected and replaced with fresh medium at 5 minutes. After filtration and appropriate dilution absorbance of collected sample was measured by UV-VIS spectrophotometer at 220 nm.

Preparation of hydralazine mouth dissolving tablet

Preparation of hydralazine mouth dissolving tablet by using superdisintegrants

The critical parameters to formulate a mouth dissolving tablet are the choice of superdisintegrant and optimization of concentration of superdisintegrant. The main criterion for mouth dissolving tablets is to disintegrate or dissolve rapidly in the oral cavity within 15 seconds to 1 minute. The mouth dissolving tablets of hydralazine were prepared by using

superdisintegrants in different ratios. The ingredients were mixed homogenously and co-grounded in a glass mortar and pestle (except talc and magnesium stearate). Finally talc and magnesium stearate were added and mixed for 5 minutes. The mixed blends of hydralazine with other excipients were compressed using single punch tablet machine.

Evaluation of tablet blend

The characterization of mixed blend done for the flow property of powder that are Micromeritic properties (Bulk density and tapped density) were determined using a bulk density apparatus and Flow properties **(**Angle of repose, compressibility index and Hausner ratio) were evaluated as per methods described in USP.

Characterization of mouth dissolving tablets

After compression of powder, the tablets were evaluated for physical organoleptic characteristics like color, odor, taste, diameter, thickness, hardness, friability, disintegration time, and wetting time.

General appearance

The general appearance of a tablet, its visual identification and over all 'elegance' is essential for consumer acceptance. Various parameters included are tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws.

Tablet thickness

Tablet thickness is an important characteristic in reproducing appearance and also in counting by suing filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer.

Uniformity of weight

USP procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be satisfactory method of determining the drug content uniformity.

Table no. 4: Weight variation limits for tablets as per USP.

Average of tablets (mg)	Maximum % difference allowed
130 or less	10
130-324	7.5
More than 324	5

Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet, the resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness.[108] Hardness of the tablet of each formulation was determined using Pfizer Hardness Tester.

Friability

Friability of the tablets was determined using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inch in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed. The friability (F %) is given by the formula:

$$F\% = \left(1 - \frac{Wo}{W}\right) X 100$$

Where, W_0 is weight of the tablets before the test and W is the weight of the tablets after test.

***In-vitro* disintegration test**

The *In Vitro* disintegration time was determined using Disintegration Test Apparatus. A tablet was placed in each of the six tubes of apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

Wetting time

The method was followed to measure tablet wetting time. A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small Petri dish (ID = 65 cm) containing 6 ml of Sorenson's buffer (pH 6.8), A tablet was put on the paper, and the time for the complete wetting was measured. Three trials for each batch were performed and the standard deviation was also determined.

In-vitro dispersion time

In Vitro dispersion time was measured by dropping a tablet in a glass vessel containing 6 ml of Sorenson's buffer (pH 6.8). Three tablets from each formulation were randomly selected and in vitro dispersion time was performed. After compression of powder, the tablets were evaluated for physical organoleptic characteristics like colour, odour, taste, thickness, hardness, friability, disintegration time and wetting time.

Content uniformity

Ten randomly selected tablets were weighed and average weight was calculated, the tablets were powdered in a glass mortar pestle[112]. The weight equivalent to 5 mg hydralazine was weighed. The weighed amount was dissolved in 5 ml of methanol in separate volumetric flask using magnetic stirrer, the volume was adjusted to 100 ml, with 50% of ehanol and the solution was filtered. An aliquot of 1.0 ml from these solutions was diluted to 10 ml Sorenson's buffer (pH 6.8) in separate volumetric flask. The content in each formulation was determined spectrophotometrically at 220 nm.

In-vitro dissolution studies

In Vitro dissolution studies for all the fabricated tablets was carried out using USP paddle method at 50 rpm in 900 ml of 50% ethanol as dissolution media, maintained at 37±0.5^{o}. 5 ml aliquot was withdrawn at the specified time intervals, filtered through Whatman filter paper and assayed spectorphotometrically at 220 nm. An equal volume of fresh medium, which was prewarmed at 37 ^{O}C, was replaced into the dissolution media after each sampling to maintain the constant volume throughout the test. The various kinetic treatments were given to the dissolution data. The *in vitro* permeation data obtained were subjected to a zero order and first order kinetics to understand the release profile and release mechanism. When a graph of the cumulative percentage of the drug released from the tablet against time is plotted, zero order release is linear in such a plot, indication that the release rate is independent of concentration.

Comparison of release with marketed tablets

Dissolution rate study was conducted for conventional marketed tablet Ambien (5mg). The various kinetic treatments were applied to the dissolution data. The *in vitro* permeation data obtained were subjected to a zero order and first order kinetics to find the release profile and release mechanism and to compare it with the optimized FDT formulation (FDT2)

RESULTS AND DISCUSSION

Drug characterization

Physical properties of pure hydralazine

Table no. 5: Table of drug (Hydralazine) properties.

S. no.	Properties	Properties reported	Properties observed
01	Color	Yellow	Light Yellow
02	Odor	Odorless	Odorless
03	Taste	Bitter	Bitter
04	Physical State	Crystalline powder	Crystalline powder
05	Melting Point	273 ^{0}C	270 ^{0}C

Determination of solubility

Table no. 2: Solubility determination.

S. no.	Solvents	Solubility observed
1	Ethanol	Freely soluble
2	Water	Soluble
3	0.1N HCl	Soluble
4	0.1N NaOH	Soluble
5	Methanol	Freely soluble

Scanning for ultraviolet absorption maxima (λmax)

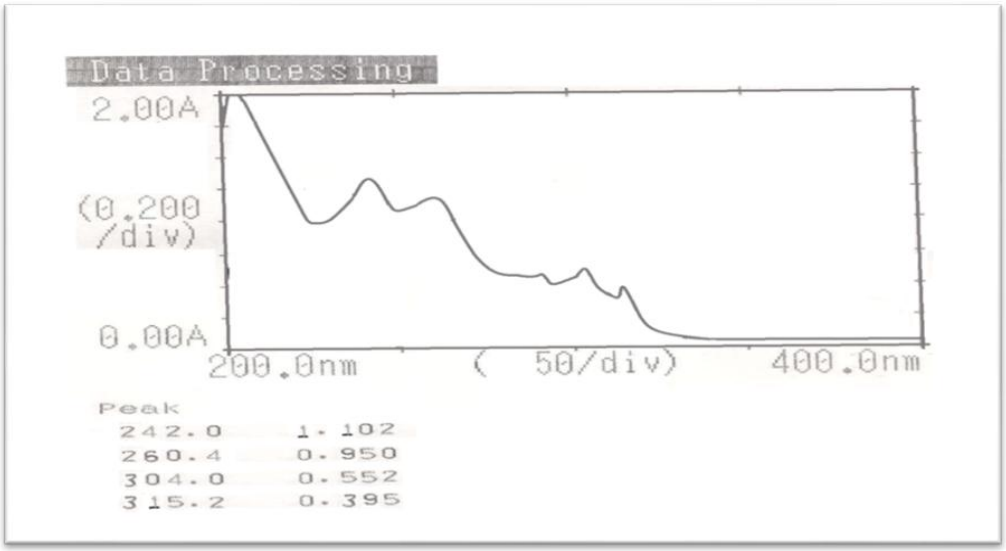

Figure no. 3: Scanning for ultraviolet absorption maxima.

Drug polymer interaction studies

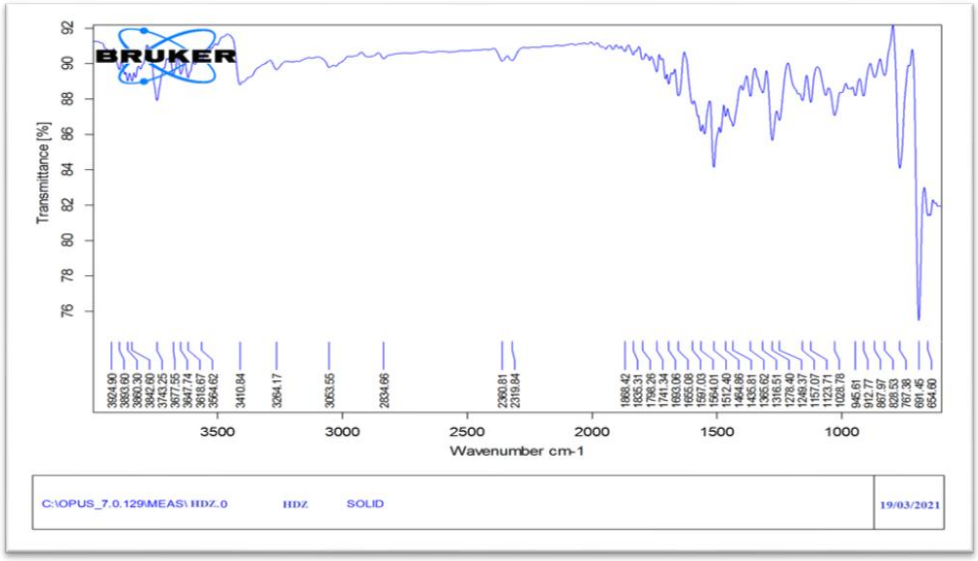

Figure no. 4: FT-IR spectrum of hydralazine HCl.

Preformulation Study

6.1.2.1 Preparation of calibration curve

Table no. 7: Calibration curve data of hydralazine HCl.

S. no.	Concentration (µg/ml)	Absorbance
1.	0	0
2.	2	0.094
3.	4	0.184
4.	6	0.278
5.	8	0.362
6.	10	0.452

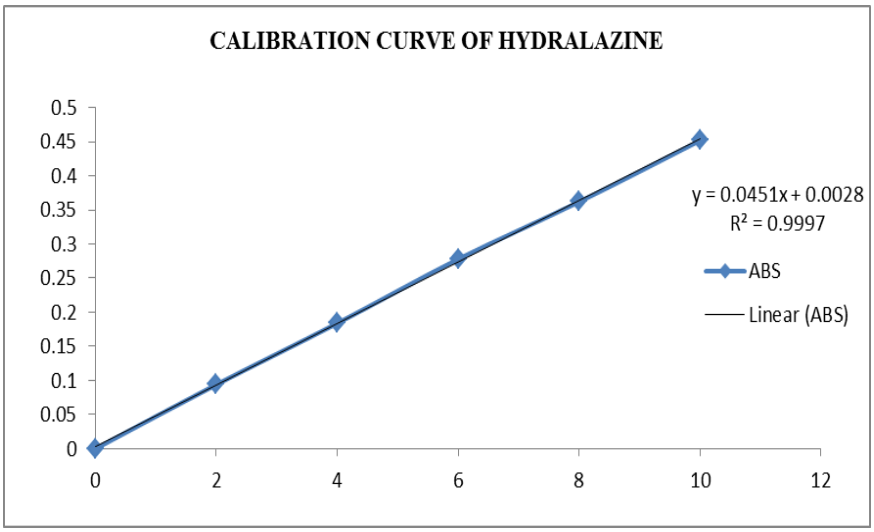

Figure no. 5: Calibration curve of hydralazine HCl.

Result: linear equation**: y = mx + C**

y = 0.045x + 0.002

Where;

y = absorbance of sample,

m = (slop) =0.045

x = concentration of sample (to be know)

C = constant = 0.002

Drug polymer interaction studies

Table no. 8: Drug-Polymer interaction studies.

Mixtures	Physical Change			IR Peak
	Liquefaction	Clumping	Color Change	
Drug	-	-	-	1637 1505 1134
Drug + Ac-di-sol	-	-	-	1636 1504 1133
Drug+crospovidone	-	-	-	1637 1499 1135
Resinate	-	-	-	1636 1505 1134

Development of method of taste masking of hydralazine

Determination of threshold bitterness concentration of hydralazine HCl

A panel of six healthy human volunteers (age 20-25) was selected. A series of solutions of hydralazine in 0.1 M hydrochloric acid of concentrations 10, 20, 30, 40, and 50 µg/ml were prepared. The volunteers hold 10 ml of each solution in oral cavity for 60s and rated the taste on a scale from 0 to 4 (0: no bitterness, 1: threshold bitterness, 2: bitter, 3: moderate bitterness and 4: strong bitterness). Rinsing the mouth by distilled water and a gap of 30 min were applied between successive tests. Based on the opinion of the volunteers, threshold bitterness concentration of hydralazine was judged.

Taste masking by formation of complexes with ion exchange resins (Resin activation)

Batch method was used to prepare drug resin complex. Ion exchange resins Tulsion-335 was swelled with deionised water for an hour and then washed with 1N hydrochloric acid and 1N sodium hydroxide in order to remove impurities (alkali and acidic impurities). The treated resin was washed several times with freshly prepared deionized water to remove the traces of

acid or alkali. This treated resin was kept in oven for 12 h at 50^0C. The dried activated resin was kept in desiccator until in use.

Effect of various parameters on Drug-resin adsorption

Table no. 9: Effect of concentration of resin on drug loading.

D:R	Absorbance	Drug percentage
1:1	0.281	33.42
1:2	0.203	36
1:3	0.176	39.98
1:4	0.141	40.87

Table no. 10: Effect of swelling by stirring Speed and Time.

Time (min)	50 rpm		100 rpm	
	Absorbance	%Drug Loading	Absorbance	%Drug Loading
15	0.118	26.92	0.120	27.34
30	0.128	29.04	0.176	31.84

Table no. 11: Effect of complexation time on drug loading.

Time (h)	Absorbance	% Drug loading
1	0.102	23.16
2	0.118	26.89
3	0.153	34.62
4	0.190	43.21
5	0.194	43.92

Table no. 12: Effect of pH on drug loading.

pH	1 h		2 h		3 h		4 h	
	Abs	% Drug loading	Abs	% Drug loading	Abs	% Drug loading	Abs	%Drug loading
1.2	0.394	6.81	0.519	11.76	0.765	17.33	0.839	19
6.8	0.172	39.05	0.199	45.14	0.212	48.10	0.251	57
7.4	0.150	33.47	0.165	39.13	0.180	42.81	0.186	44.12

Optimized formulation of drug resinate

The obtained resinate was separated by vacuum filtration and dried in vacuum desiccator.

Preparation of non bitter Drug-resin granules

Drug was mixed with Tulsion 335 (1:3) with the help of glass mortar and pestle. Then 10% ethanol was added to mixture as granulating agent. The dump mass was converted into the granules by passing through sieve number 24. After granulation, they were dried at 50^0C in tray drier.

Evaluation of drug Resinate and Granules

***In-vivo* taste evaluation**

Table no. 13: *In-vivo* taste evaluation.

Volunteer	Taste Evaluation		
	Drug	Granules	Resinate
1	4	2	0
2	4	3	0
3	4	1	0
4	4	1	0
5	4	2	0
6	3	2	0

0: no bitterness, 1: threshold bitterness, 2: bitter, 3: moderate bitterness 4: strong bitterness

Physical evaluation of granules

Table no. 14: Physical evaluation of Resinate and Granules.

Parameters	Resinate	Granules
Bulk Density (gm/cm^3)	0.611	0.628
Tapped Density (gm/cm^3)	0.702	0.694
Compressibilty Index (%)	12.962	9.523
Hausners Ratio	1.148	1.105
Angle of Repose	23.64	21.817

Determination of *in-vitro* drug release from resinate

Table no. 15: *in-vitro* dissolution of drug release in pH 1.2, 6.8, 7.4.

Time (min)	% Drug Release from Resinate		
	pH 1.2	pH 6.8	pH 7.4
0	0	0	0
5	12.03	9.90	2.24
10	21.68	18.48	5.65
15	30.32	24.97	8.88
20	40.08	31.50	11.06
30	49.88	43.39	12.19

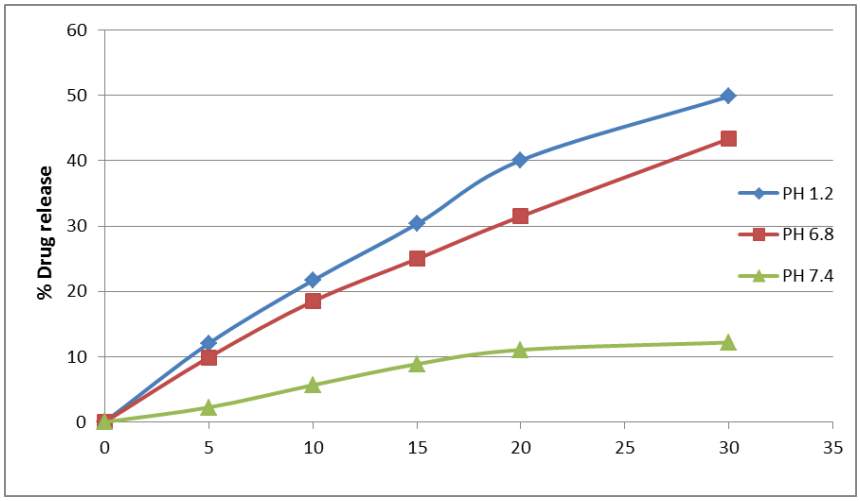

Figure no. 9: *in-vitro* Dissolution of Drug Release in pH (a) 1.2 •, (b) 7.4 ▲, (c) 6.8■

Preparation of hydralazine HCl mouth dissolving tablet

Hydralazine HCl mouth dissolving tablet preparation by using superdisintegrants

Table no. 16: Formulation of mouth dissolving tablets with resinate.

Ingredients	FDT1	FDT2	FDT3	FDT4	FDT5	FDT6
Drug resinates equivalent to 5 mg of hydralazine HCl	35 mg	35 mg	35 mg	35 mg	35 mg	35 mg
Crospovidone	3 mg	4 mg	-	-	-	-
Ac-Di-Sol	-	-	3 mg	4 mg	-	-
SSG	-	-	-	-	3 mg	4 mg
MCC	26	26	26	26	26	26
Dextrose	15	15	15	15	15	15
Lactopress	15	15	15	15	15	15
Talc	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2

Evaluation of tablet blend

Table no. 17: Evaluation of tablet blend.

Ingredients	FDT1	FDT2	FDT3	FDT4	FDT5	FDT6
Bulk Density (gm/cm^3)	0.584± 0.009	0.625± 0.007	0.611± 0.006	0.627± 0.006	0.633± 0.005	0.574± 0.012
Tapped Density (gm/cm^3)	0.666± 0.007	0.718± 0.008	0.711± 0.010	0.714± 0.011	0.715± 0.011	0.649± 0.003
Compressibilty Index (%)	12.212± 0.005	12.952± 0.005	14.051± 0.010	12.220± 0.004	11.447± 0.015	11.499± 0.004
Hausners Ratio	1.126± 0.392	1.134± 0.544	1.136± 0.765	1.112± 0.795	1.129± 1.233	1.117± 0.782
Angle of Repose	22.713± 0.953	22.931± 0.268	23.189± 0.553	23.756± 0.434	23.282± 0.754	24.231± 0.725

Characterization of mouth dissolving tablets

Table no. 18: Characterization of mouth dissolving tablets.

Ingredients	FDT1	FDT2	FDT3	FDT4	FDT5	FDT6
Thickness(mm)	2.313± 0.022	2.076± 0.121	2.329± 0.089	2.415± 0.025	2.361± 0.061	2.295± 0.066
Weight (mg)	99.133± 0.665	98.466± 0.737	99.4± 0.264	100.833± 1.450	97.233± 0.602	97.733± 0.321
Hardness (kg/cm^3)	2.713± 0.156	2.913± 0.200	3.043± 0.150	3.003± 0.090	2.800± 0.191	2.990± 0.101
Friability (%)	0.823± 0.051	0.64± 0.05	0.536± 0.030	0.626± 0.045	0.653± 0.081	0.856± 0.041
in-vitro Disintegration time (s)	51.66± 2.51	20.66± 2.08	62.66± 2.516	38.00± 3.00	66.33± 3.05	41.66± 1.52
Wetting time (s)	47.33± 6.02	18.66± 2.51	57.66± 3.51	32.33± 3.51	55.66± 6.11	38.33± 2.08
in vitro Dispersion Time (s)	57.33± 1.52	26.33± 2.08	63.63± 2.08	31.33± 2.51	68.66± 2.08	46.00± 2.64

Content uniformity

Table no. 19: Drug content in the mouth dissolving tablet of hydralazine HCl.

Formulations code	Parameters	
	Drug content (mg per Tablet)	Drug content (%)
FDT1	4.86±0.25	97.2
FDT2	4.93±0.35	98.7
FDT3	4.83±0.30	96.7
FDT4	4.96±0.42	99.2
FDT5	4.94±0.25	98.8
FDT6	4.97±0.31	99.4

***In-vitro* dissolution studies**

Table no. 20: *in-vitro* release data of hydralazine HCl tablet.

Time (min.)	Cumulative percent drug released					
	FDT1	FDT2	FDT3	FDT4	FDT5	FDT6
0.000	0.000	0.000	0.000	0.00	0.000	0.000
1.000	74.27	77.58	68.75	70.96	57.72	61.03
2.000	77.99	84.63	70.33	74.22	64.66	67.99
3.000	85.04	89.51	72.98	76.89	69.43	73.88
4.000	92.13	95.52	80.73	85.66	73.12	78.70
5.000	94.84	98.25	81.67	90.54	75.72	80.23

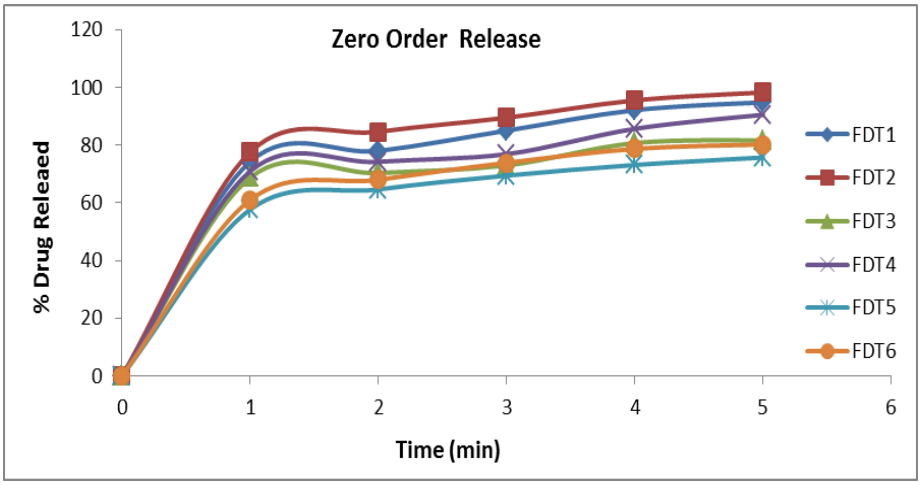

Figure no. 10: *In-vitro* release curve of hydralazine HCl Tablet-Zero order release

Log % drug retained data of hydralazine HCl tablet.

Table no. 21: *In-vitro* log % drug retained data of hydralazine HCl tablet.

Time (min.)	Log cumulative percent drug retained					
	FDT1	FDT2	FDT3	FDT4	FDT5	FDT6
0	2	2	2	2	2	2
1	1.410	1.350	1.494	1.462	1.626	1.590
2	1.342	1.186	1.472	1.411	1.548	1.505
3	1.174	1.020	1.431	1.363	1.485	1.416
4	0.895	0.651	1.284	1.156	1.429	1.328
5	0.712	0.243	1.263	0.975	1.385	1.296

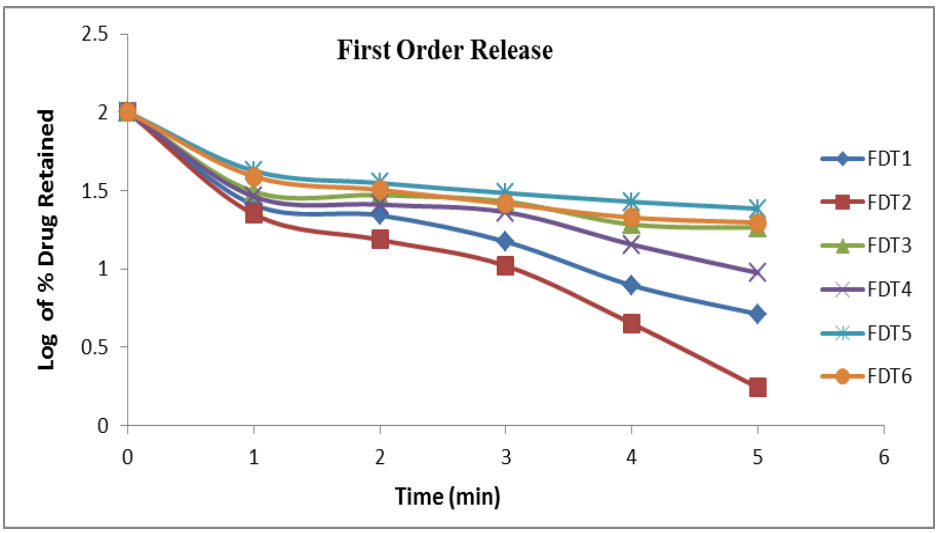

Figure no. 11: *in-vitro* drug retained curve of hydralazine HCl Tablet-first order release.

Comparision of release with marketed tablets

Table no. 22: *In-vitro* release profile of hydralazine HCl marketed tablets.

Time (min)	Cumulative % Drug Release (Marketed)	Log Cumulative %Drug Retained (Marketed)
0	0	2
1	9.53	1.95
2	18.46	1.91
3	24.64	1.88
4	28.74	1.85
5	38.33	1.79
30	43.73	1.75
60	46.37	1.73

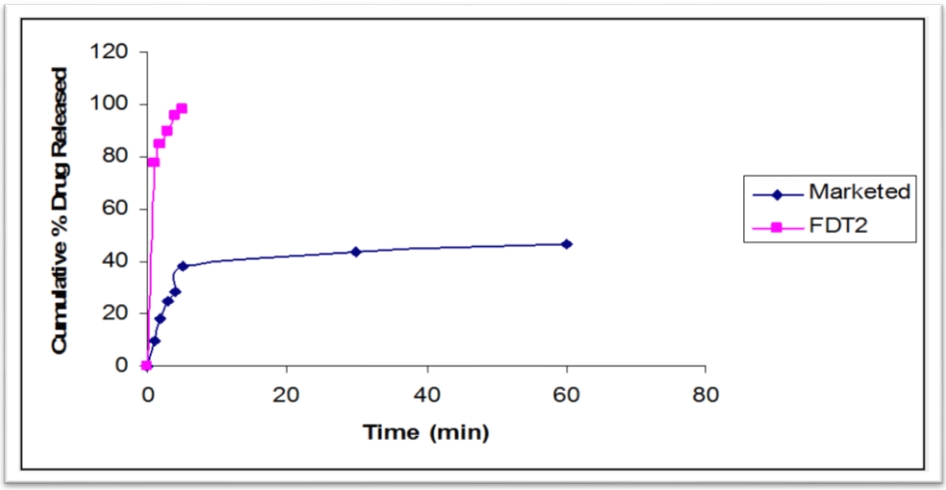

Fig. no. 12: *In-vitro* zero order release curve of FDT2 and hydralazine HCl marketed tablets.

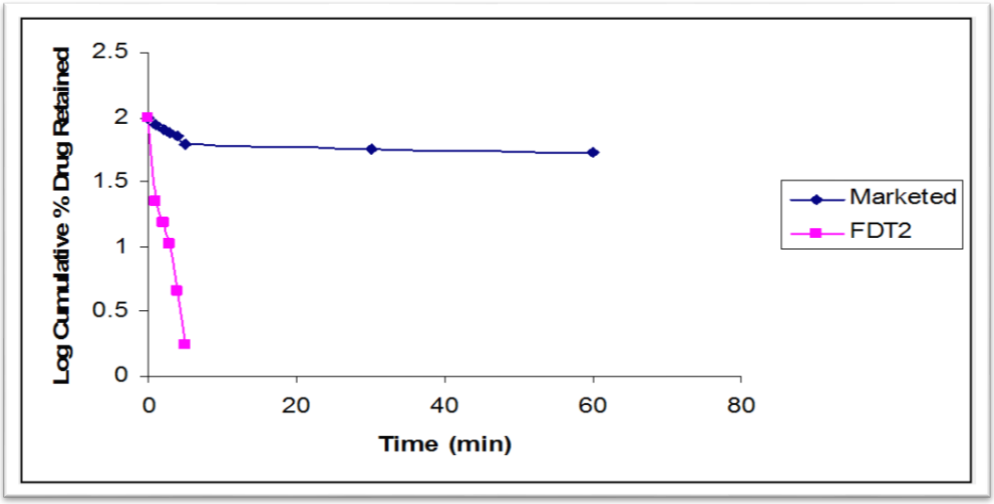

Fig. no. 13: *In-vitro* first order release curve of FDT2 and hydralazine HCl marketed tablets.

DISCUSSION

In this study, novel mouth dissolving taste masked tablets of hydralazine HCl with adequate mechanical strength were prepared, optimized and evaluated for various *in-vitro* and *in-vivo* parameters.

The obtained sample of hydralazine HCl was identified by various organoleptic, physicochemical and spectrophotometeric methods. The sample of hydralazine HCl posses similar color, odor, taste and texture as given in officials. The melting point of obtained sample was found to be 140-141^{o}C. The IR Spectra of obtained sample drug was concordant with Reference Spectra as given in Clarke's Analysis. The various peaks were depicted in FT-IR Spectra verified the authenticity of the obtained sample. The solubility of hydralazine HCl was determined in different solvent systems. The maximum solubility was found in 0.1N HCl and ethanol. The absorption maxima of hydralazine HCl were observed at 220 nm. The calibration curve of hydralazine HCl was prepared. The plot of different concentrations of hydralazine HCl versus absorbance was found to be linear in the concentration range of 10-30 µg/ml at 220 nm. The IR Spectra of the various mixtures reveal all the peaks of the drug. No significant shifts were observed on the mixing and storage. Both the drug and polymers were compatible with each other.

Threshold bitterness concentration is the minimum concentration at which bitterness starts to appear and continues to provoke after 30s. Most of the volunteers rated 20µg/ml, as the threshold bitterness concentration for hydralazine HCl. It was concluded that the taste masked form of the drug should not release more than or equal to 20 µg/ml of the drug in mouth within 2 minutes for satisfactory taste masking.

Loading of hydralazine HCl on Tulsion 335 was carried out by batch process. Highest drug loading on resin was achieved when activated with both acid-alkali treatments. The maximum drug loading was achieved at D:R(1:3) in resinates. The resin requires proper swelling time for maximum drug loading. It was concluded that a swelling time of 60 minutes was sufficient for maximum swelling of ion exchange resin. Swelling and hydration increases the rate and extent of ion exchange process. The effect of complexation time on drug loading it was found that with increase in time for stirring the solution, the drug loading gets increased and maximum drug loading was achieved at 4 h. When hydralazine HCl was loaded into resin in different pH environments, it was observed that optimum drug loading was achieved at pH 7.0 and further decreased at pH higher than this. In acidic environments

(generally pH below 4) the resin exists as free acid in an essentially nonionic state and all drug was released in filtrate and at pH 7.4 the solution becomes basic and cationic ions gets saturated with basic solution so ions cannot be attached with basic solution.

Granules show low degree of bitterness than pure hydralazine HCl. The Micromeritic properties of resinate powder and granule were determined using a bulk density apparatus and flow properties **(**angle of repose, compressibility index and hausner ratio) were evaluated as per methods described in USP. All the quality control parameters were found in range as per the specifications given in official references.

Release of hydralazine HCl from resinate in three different pH media. Resinate showed the maximum release of drug in 0.1 N HCl (pH 1.2) due to cleavage of bond between the drug and resin. At pH 7.0 similar condition to saliva showed less release of drug confirms that the removal of bitter taste of drug. At pH 7.0 in time interval of one minute 0.05 mg drug was released which has not enough bitter taste sensation. The neutral medium (pH 7.4) showed very less drug release.

After compression of powder, the tablets were evaluated for their physical organoleptic (colour, odour, taste) and quality control parameters (thickness, hardness, Friability, disintegration time and wetting time). All the formulations were white in colour, odorless, flat in shape with smooth surface having zero defects. The prepared tablets were elegant and also free from any surface texture problems.

The thickness of the tablet was found 2.076 to 2.415 mm. The average weight of the prepared tablet was found 97.233 to 100.833 mg. So it was predicted that all the formulation exhibited uniform weight with low standard deviation values within the acceptable variation as per USP. The hardness of the prepared tablet varied from 2.713 to 3.033 kg/cm^2, which showed tablets have satisfactory strength to withstand with the applied mechanical shocks. Friability can affect the tablet weight and content uniformity. The friability of all the formulation was found to be less than 1.0 %, which showed the durability of the prepared tablets, resistance to loss of weight indicates the tablet's ability to withstand abrasion in handling, packaging and shipment.

A super disintegrant was added in the formulations to facilitate a breakup or disintegration of the tablet when it contacts with water or saliva in mouth. Super disintegrants act by drawing

the water into the tablet causing swelling and burst apart of the tablet. The tablets with Crospovidone disintegrated faster than the tablets containing Ac-Di-Sol and sodium starch glycolate. The *in vitro* disintegration time of all the formulations varied between 20.66 ± 2.08 s to 66.33 ± 3.05 s.

The in vitro wetting time was also studied to know the process of disintegration. The in vitro wetting time of all the formulations varied between 18.66 ± 2.51 to 57.66 ± 3.51. The wetting properties of the superdisintegrant were depend upon their concentration and the results showed that as the concentration of the superdisintegrant increased the time taken for swelling was reduced. The wetting time was minimum with Crospovidone followed by Ac-Di-Sol and sodium starch glycolate. The same sequence was observed in all the parameters related to disintegration of the tablet.

The drug content of all formulations was determined spectrophotometrically at 220 nm. It varied from 4.86 ± 0.25 to 4.97 ± 0.35 mg per tablet. The uniformity of drug content was also shown the uniformity of tablet punching process.

In-vitro drug release experiments were performed at 37±0.5^{o}C in paddle type dissolution apparatus. The results showed that all the formulations release the drug within 6 to 7 minutes. The maximum drug release was found in formulation FDT2 (98.747%).

The order of drug release was found to be:

FDT2 >FDT1 >FDT4 >FDT3 >FDT6 >FDT5

The formulation with crospovidone showed maximum release than the tablets with Sodium starch glycolate and Ac-Di-Sol. The experiment proved that the disintegration release was rate-limiting step from the tablet. So release of drug and release rate was higher from these tablets. From the observed data, it can be clear that less time in disintegration increases the release rate of hydralazine HCl from Mouth Dissolving Tablet. Next the release data obtained were subjected for the kinetic treatment to know the type and order of drug release.

CONCLUSION

The obtained hydralazine HCl was concordant with reference specifications. The volunteers rated resinate as tasteless and agreeable complex. Mouth dissolving tablet was prepared by addition of superdisintegrants (Ac-Di-Sol, Sodium starch glycolate and Crospovidone). On applying zero order and first order dissolution kinetic treatments, it was found that all the

prepared tablets followed first order kinetics. Hence, mouth dissolving tablets of resinate can be successfully prepared by superdisintegrants, maintaining their disintegration time less than 1 minute, which provide faster effect and better patient compliance. These tablets may be helpful for geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. Thus it was concluded that the method designed for drug resinate complexation and tablet formulation is simple, rapid, cost effective and highly efficient.

CONFLICTS OF INTEREST

There are no conflicts of interests.

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