Formulation, Evaluation and Optimization of Mouth Dissolving Tablets of Hydralazine Hydrochloride using Novel Co-Processing Technique

Geetika Sharma, Rupinder Kaur, Ajay Kumar, Sukhdev Singh, Upendra. K. Jain

Abstract - The objective of this research was to formulate fast dissolving tablet of Hydralazine hydrochloride for rapid action. Hydralazine hydrochloride is a direct acting smooth muscle relaxant used to treat hypertension. It belongs to the hydrazinophthalazine class of drugs. Direct Compression method was adapted to prepare the tablets by using a 3^2 full factorial design. Co-Processing of excipients could lead to formation of excipients with superior properties compared with the simple physical mixture of their components or with individual components[1]. FT-IR and Dissolution studies revealed that there was no physico-chemical interaction between Hydralazine hydrochloride and other excipients. All formulations are evaluated for pre-compression and post-compression parameters, wetting time, weight variation, and friability. F7 batch contain Hydralazine hydrochloride (Drug), SSG (4%), Crosspovidone (2%) and other excipients. F7 batch was the optimized batch since it showed of Disintegration time (17sec), friability (0.91%) and %Drug release (98.70%).

Key Words: Hydralazine hydrochloride, Sodium Starch Glycolate, Crosspovidone, MCC, Co-Processing.

I. INTRODUCTION

The concept of Fast Dissolving Drug Delivery System emerged from the desire to provide patient with conventional mean of taking their medication. Difficulty in swallowing (Dysphasia) is a common problem of all age groups, especially elderly and pediatrics.[2] Mouth dissolving tablets are prepared by many techniques, mainly direct compression, lyophilization & moulding but most simple and cost effective technique is the direct compression technique.[3, 4]

Hydralazine hydochloride (1-hydrazinylphthalazine) is a direct smooth muscle relaxant used to treat hypertension by acting as a vasodilator. Hydralazine increases cyclic guanosine monophosphate (cGMP) levels, increasing the activity of protein kinase G (PKG) muscle. This results in blood vessel relaxation. It has an elimination half-life is 2-4 hrs. It is soluble in water (1g/125ml), slightly soluble in methanol (1g/500ml), Insoluble in phosphate buffer (1g/MT 1000ml). [5, 6] The objective of this study was to formulate Hydralazine hydrochloride mouth dissolving tablet using direct compression technique and to clarify the effect of different superdisintegrants like Crosspovidone, Sodium starch glycolate (SSG), on the disintegrating and dissolution properties of tablets.

II. MATERIALS AND METHODS

Hydralazine hydrochloride was purchased from sigma laboratories, via Magus Laboratories, Mohali. Microcrystalline cellulose (Avicel PH-102), Mannitol (Pearlitol SD 200) was purchased from All well pharmaceutical company Chandigarh. Sodium starch glycolate and crosspovidone were purchased from Magus Laboratories Mohali. All the other chemicals used were of analytical grade and were arranged form college's chemical and drug store.

III. PREFORMULATION STUDIES

It includes drug characterization. Capillary fusion method was used to determine the melting point of Hydralazine hydrochloride. The determined melting point of Hydralazine hydrochloride was 172^oC which is identical to the theoretical value which is $172\text{-}173^0$ C. Thus, indicated the identity and purity of drug. Solubility studies were carried out by using Shake Flask Method and U. V spectrophotometer. Apparent Partition Coefficient of drug was calculated and was comparable to literature value.[7]

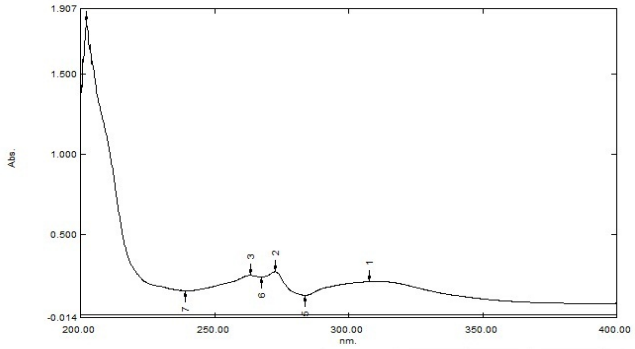
Drug excipients interaction studies

Storage at accelerated conditions (40 ± 2^o C/75 ± 5%RH) was done. FTIR technique has been used here to study the physical and chemical interaction between drug and excipients. FTIR of drug alone, drug and MCC (1:1), drug and MCC (1:5), drug and SSG (1:1) and drug and SSG (1:5) were taken respectively The result obtained matched the peaks of different chemical groups in drug and were accurate.

Formation of Calibration Curve

Standardization of the drug was carried out using UV spectrophotometer. Solubility analysis of drug in various

solvents including water, phosphate buffer pH 7.2, and organic solvents like methanol. To establish linearity of the proposed method, seven separate concentrations of the solution of Hydralazine hydrochloride 1- 40µg.ml^{-1}, 2- 10 µg.ml^{-1}, 2-12 µg.ml^{-1} in water, methanol and Phosphate buffer pH 7.2 were prepared from stock solution and analyzed.. The data was subjected to least square regression analysis. ANOVA test (one-way) at 95% level of significance was performed based on absorbance values observed for each pure drug concentration during the replicate measurements of the standard solution. (Fig 1, 2, 3).



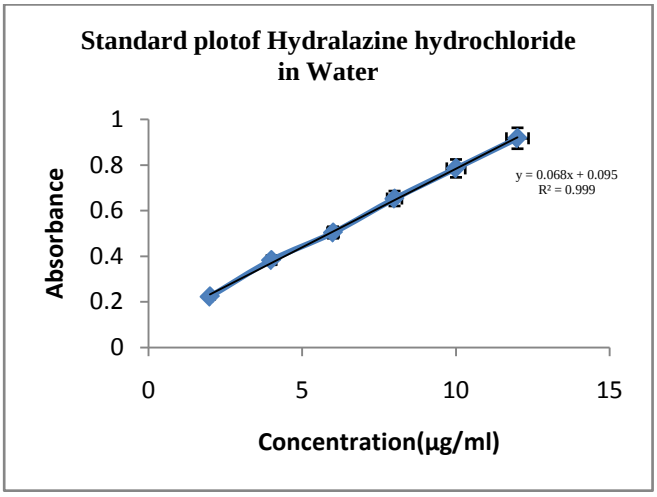
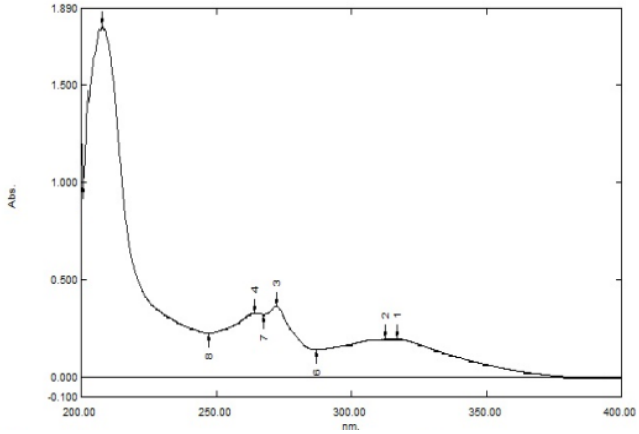


Fig. 1



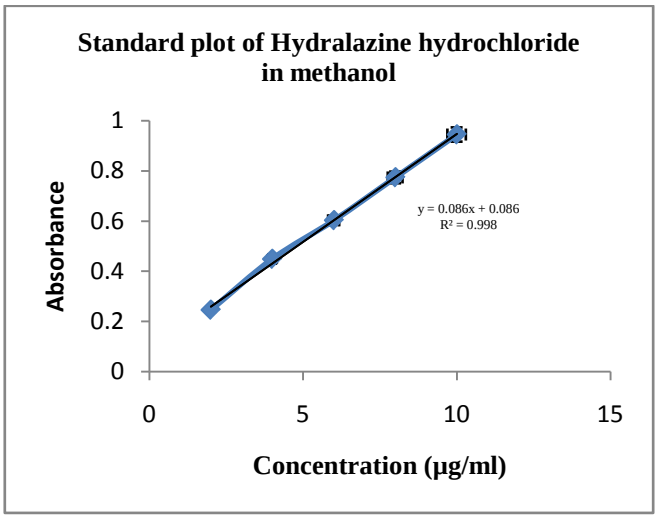
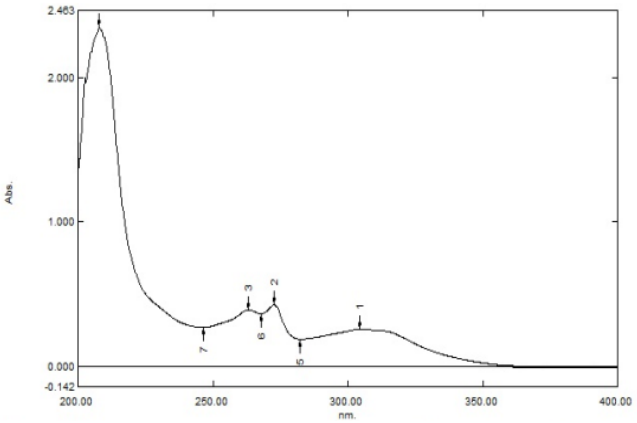


Fig. 2



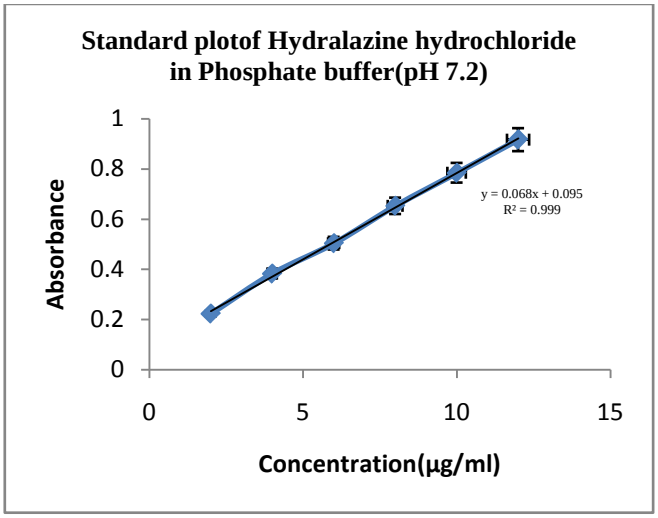


Fig. 3

IV. PREPARATION OF MDT'S BY DIRECT COMPRESSION METHOD

Mouth dissolving tablets of Hydralazine hydrochloride were prepared using different excipients for physical as well as co processed mixture and then evaluated for various parameters

to select the best combination for preparation of Hydralazine hydrochloride mouth dissolving tablet. Physical and Co-processed mixtures were prepared in ratios from 1:1, 1:2 and 1:3. The temperature was maintained between 50ºC and 60ºC, and stirring was continued till most of isopropyl alcohol evaporated. The wet coherent mass was granulated through 60-mesh sieve. The wet granules were dried in a tray dryer at 60ºC for 20 minutes. The prepared co processed superdisintegrants were evaluated for the mass-volume relationship, swelling properties and flow properties as shown in Fig. 4.

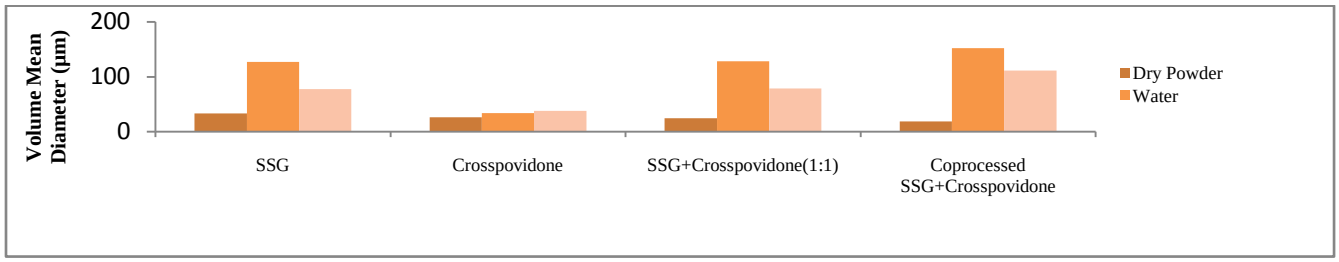
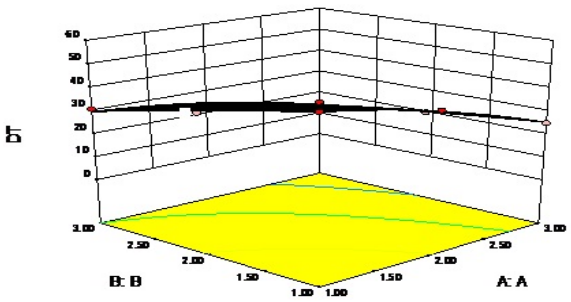


Fig. 4

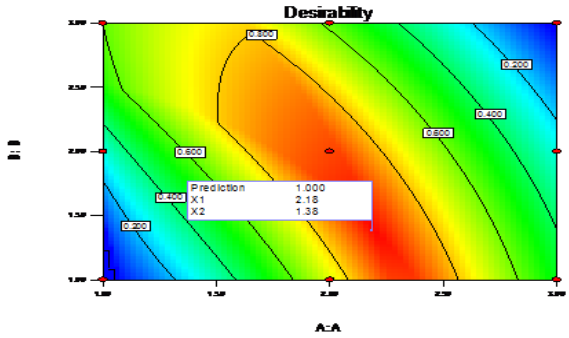
V. OPTIMIZATION OF FORMULATION [8, 9]

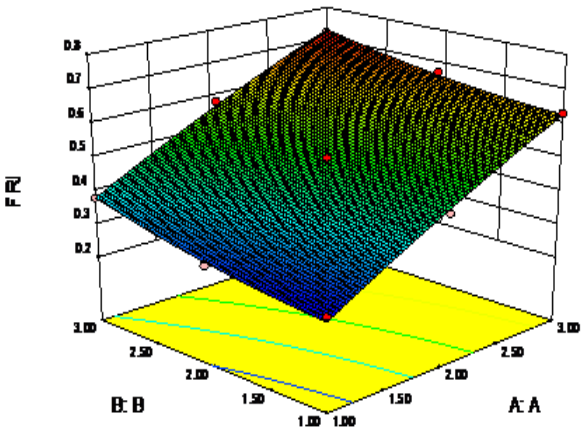
Factorial Consideration

The experimental design was a two factor three level (3^2) full-factorial design, and nine formulations were prepared. The amount of superdisintegrants was optimized for dependent variables: disintegration time and percent friability. The low (-1), medium (0) and high (1) are the values of X_1 (SSG) and X_2 (Crospovidone) respectively. Responses were analyzed for ANOVA. In order to investigate the factors systematically and optimize the tablet for DT 35 seconds and % F less than 0.5%, a factorial design is applied in the present investigation. The high values of correlation coefficient for disintegration time, 0.9908 and percentage friability, 0.9991 indicate good fit. Values of 'p' less than 0.05 indicate model terms are significant. In this case both the models generated for disintegration time and % friability were significant.



The model F value of 64.94 for disintegration time and 69.270 for friability and high R^2 values suggested that these models are significant. There is only 0.01% chance that a 'Model F-value' this large could occur due to noise. A ratio greater than 4 is desirable.





The ratios of 25.025 and 76.368 respectively for DT and % F models indicated an adequate signal for each. When higher percentage of sodium starch glycolate is used, the water uptake and subsequent disintegration are thus facilitated. It is

obvious that in the presence of higher percentage of disintegrant crospovidone, wicking is facilitated. Results were shown in response surface plot and contour plots for disintegration time and percentage friability Fig 5 and Table 1, 2.

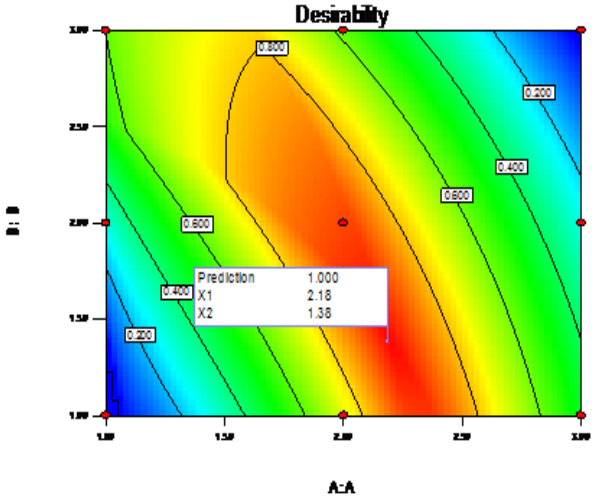


Fig. 5

Table 1: Factorial Design based Hydralazine hydrochloride MDT's

Batch code	X_1 (mg.)	X_2 (mg.)	DT (S)	Friability (%)
F11	-1	-1	31	0.38
F12	-1	0	40	0.44
F13	-1	1	34	0.5
F14	0	-1	20	0.67
F15	0	0	39	0.29
F16	0	1	25	0.63
F17	1	-1	15	0.72
F18	1	0	49	0.27
F19	1	1	23	0.58

Coded values	Actual Values	
	X_1	X_2
-1	1	1
0	2	2
1	3	3

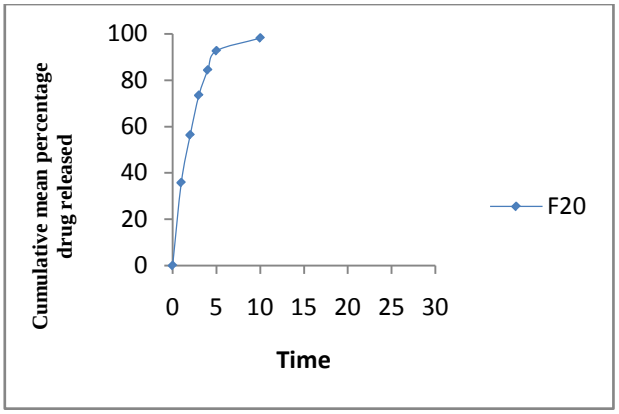
Table 2: Evaluation of optimized hydralazine hydrochloride MDT's (F_{20})

Ingredients	Amount (mg)
Hydralazine hydrochloride	10
SSG	2.18
Crospovidone	1.38
MCC (Avicel PH-102)	98.94
Mannitol (Pearlitol SD 200)	30
Sodium saccharine	3
Talc	3
Lactose	1.5

Parameteres	Results
Hardness (kg/cm^2) (Mean±SD)*	3.21±0.12
Friability (%) (Mean±SD)**	0.50±0.01
Disintegration time (sec) (Mean±SD)***	30.66±0.49
Wetting time (sec) (Mean±SD)****	24.29±0.08
Drug Content (%) (Mean±SD)****	96.28±0.23
Weight variation (mg) (Mean±SD)[a]	150.35±0.001
Dispersion time (sec) (Mean±SD)***	44.65±0.31

VI. CONTENT UNIFORMITY AND IN VITRO DISSOLUTION STUDY [10, 11, 12]

In vitro dissolution study of optimized formulation and marketed tablet were carried out using USP paddle method at 50 rpm in 900 ml of Phosphate buffer (pH 7.2) as dissolution media, maintained at 37±0.5°C. 5 ml of aliquot was withdrawn at the specified time intervals (1 minute) and assayed by U.V at 272 nm. The obtained data from in vitro Drug release study are tabulated and represented graphically as shown in Fig 6. Results indicated that the plot of log cumulative % drug retained vs. time of formulation was fairly linear as indicated by their high regression. The results of dissolution profile for the optimized formulation are shown in Table 3.



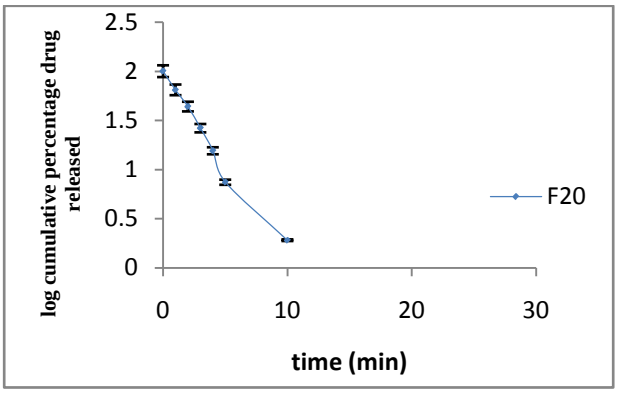


Fig. 6

Table 3: Dissolution release profile of optimized mouth dissolving tablet

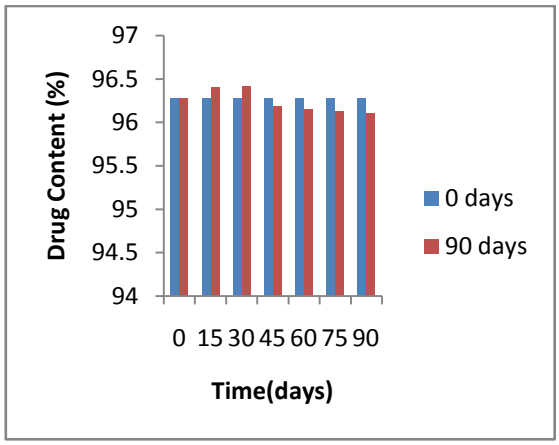
Time (min)	Cumulative Mean Percent Drug Released (Mean±SD)*	Log Cumulative Mean Percent Drug Released (Mean±SD)**
0	0	2
1	35.72±1.98	1.81+0.29
2	56.26±2.06	1.64±0.31
3	73.42±2.02	1.42±0.30
4	84.30±1.86	1.19±0.27
5	92.61±1.95	0.87±0.29
10	98.10±1.88	0.28±0.27

VII. KINETIC OF DRUG RELEASE

The data from the *in vitro* study of optimized formulations was fitted to the above mentioned kinetic model to determine kinetic of drug release. It was found the release from optimized MDT follow first order kinetics as predicted by their higher correlation coefficient value (R^2).

VIII. STABILITY STUDIES [13, 14, 15]

In order to access the long term stability, the optimized mouth dissolving tablets of hydralazine hydrochloride were stored at (40± 2°C/75±5% RH) for a period of 3 months. The tablets were withdrawn after a period of 15 days and analyzed for physical characterization and drug content. FDA has set a public standard of $f2$ value between 50 to 100 indicate similarity between two dissolution profiles. No significant difference was observed in release profile of optimized formulation (F20) as shown in Fig.7. The value of similarity (f2) and dissimilarity (f1) factor for in vitro release study suggest that profile of optimized formulation (F20) matches with that of theoretically predicted; since f1 and f2 was less than 15 and greater than 50 were obtained.



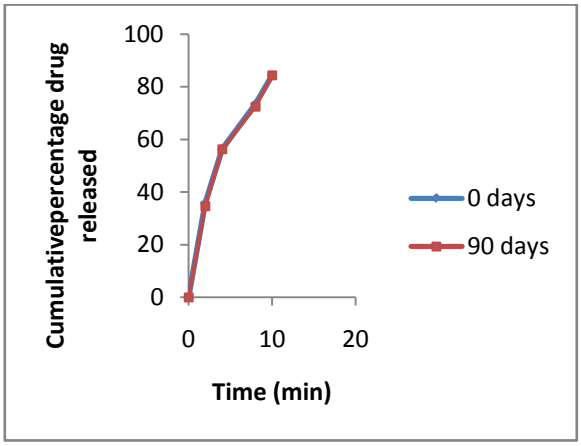


Fig. 7

IX. CONCLUSION

Co-processing of excipients could lead to formulation of excipients with superior properties compared with the sample physical mixture of their components or individual components. The use of physical mixtures resulted in increased friability probably due to low compressibility of excipients. It may be concluded that co-processed superdisintegrant is superior to physical mixture for formulating the MDTs. Full factorial design (3^2) was used for the optimization of formulation to get DT equals to 35 seconds and friability 0.5%. The disintegration time and percentage friability for the 9 batches (F11- F19) showed a wide variation. The data clearly indicate that the disintegration time and percentage friability values are strongly dependent on the selected independent variables.

REFERENCES

[1] Konapure AS, Chaudhari PS, Oswal RJ, Kshirsagar SS, Antre RV and Chorage TV: Mouth dissolving tablets-an innovative

technology. International Journal of Applied Biology and Pharmaceutical Technology 2011; 2(1): 496-503.

[2] Kumar MV, Sethi P, Kheri R, Saraogi GK and Singhai AK:Orally disintegrating tablets: a review International Research J of Pharmacy 2011; 2(4): 16-22.

[3] Chaudhary SA, Chaudhary AB and Mehta TA: Excipients updates for orally disintegrating dosage forms. International J of Research in Pharmaceutical Sciences 2010; 1(2): 103-207.

[4] A Textbook of Pharmaceutics "Analytical Profiles of Drug Substance" volume 8, third edition by Chester E. Orzech, Norris G. Nash and Raymond D. Daley.

[5] Klaus F, editor. Analytical profile of drug substances and excipients.vol-8, Academic press. Inc; 1981. p. 289-312.

[6] Drug bank. Www.drugbank.ca. http://www.drugbank.ca/drugs/DB00999

[7] Indian Pharmacopoeia. Dr. Nityanand, Chairman, 5th edition I. P. 2007

[8] Formulation and Characterization of Hydralazine Hydrochloride Biodegraded Microspheres for Intramuscular Administration, Nanjwade et al. J Bioanal Biomed 2011, 3:1.

[9] Stability of Hydralazine Hydrochloride in Both Flavored and Nonflavored Extemporaneous Preparations, Claudia C. Okeke, PhD,Thomas Medwick, PhD, Graham Nairn, PhD, Shaila Khuspe, BSc, Lee T. Grady, PhD.

[10] Jean-Pierre Schirmann, Paul Bourdauducq "Hydrazine" in Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH, Weinheim, 2002. doi:10.1002/14356007.a13_177.

[11] Erk N. Three new spectrophotometric methods applied to the simultaneous determination of hydralazine hydrochloride. 2003; 58(8): 533-541.

[12] United States Pharmacopoeia. Rockville.MD: USP Convention, Inc .32 revision , NF 27; 2009.

[13] Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products U.S. Department of Health and Human Services ,Food and Drug Administration Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) November 2003 ICH Revision 2

[14] Shah VP. Tsong Y, Sathe P. *In vitro* dissolution profile comparison - statistics and analysis of the similarity factor, f2. Pharm Res. 1998; 15: 889-896.

[15] Pebley WS, Jager NE, Thompson SJ, Rapidly disintegrating tablets, US Patent No.5, 298261, 1994, 5-17.