FUNDAMENTA EVALUATION OF MULTI -LAYERED TABLETOF DIVALPROEX SODIUM

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Abstract:- The optimized immediate release layer (IF6) with highest in vitro release of 98.11 was selected for bi-layered tablet formulation. HPMC K4M and HPMC K100M polymer used to retard the drug release from sustained release layer in different proportion and combination and evaluated for physical parameter along with in vitro drug release studies.. The optimized sustained releaselayer (SF8) which extends the Divalproex sodium release more than 18 hrs was selected. *In vitro* drug release studies were performed using USP type II apparatus (paddle method) in 900 ml of phosphate buffer pH 6.8 at 100 rpm. Finally Bi-layered tablets were prepared by double compression of selected sustained release layer and immediate release layer of Divalproex sodium. The tablets were evaluated for hardness, thickness, weight variation, friability, drug content uniformity and *in vitro* drug release. All the physical parameters were in acceptable limit of pharmacopeial specification. The stability studies, shown the bi-layer tablet was stable at 40^0C/ 75% RH for a period of 3 months.

Keywords:- Pharmacopeial Specification, Release Layer, Divalproex Sodium

I. INTRODUCTION

Drug in the outside layer exposed to the bathing solution is dissolved first and then diffuses out of the matrix. This process continues with the interface between the bathing solutionand the solid drug moving toward the interior. It follows that for this system to be diffusion controlled, the rate of dissolution of drug particles within the matrix must be much faster than the diffusion rate of dissolved drug leaving the matrix. Derivation of the mathematical model to describe this system involves the followingassumptions:

- A pseudo-steady state is maintained during drug release.
- The diameter of the drug particles is less than the average distance of drug diffusionthrough the matrix;
- The bathing solution provides sink conditions at all times. The release behavior for thesystem can be mathematically described by the following equation:

$$DM/Dh = C_O . Dh\text{-}C_S/2 \quad (1)$$

Where,
DM = change in the amount of drug released per unit area
Dh = change in the thickness of the zone of matrix that has been depleted of drugC_O = total amount of drug in a unit volume of matrix
C_S = saturated concentration of the drug within the matrix.

1.1 DIFFUSION THEORY

$$DM = (D. C_S / h).Dt \quad (2)$$

Where, Dm = Diffusion coefficient in the matrix
h = thickness of the drug-depleted matrix
Dt = change in time.

By combining equation 1 and 2 and integrating;

$$M = [C_S . Dm. (2C_O - C_S). t]^{1/2} \quad (3)$$

When the amount of drug is in excess of the saturation concentration, then:

$$M = [2C_S . Dm. C_O . t]^{1/2} \quad (4)$$

Equation 3 and 4 relate the amount of drug release to the square-root of time. Therefore, if a system is predominantly diffusion controlled, then it is expected that a plot of the drug release vs. square root of time will result in a straight line. Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores. The volume and length of the opening must be accounted for in the drug release from a porous orgranular matrix:

$$M = [Ds.Ca.p/T.(2C_O - p.C_a) t]^{1/2} \quad (5)$$

Where,
p = Porosity of the matrix, t = Tortuosity, Ca = solubility of the drug in the release medium
Ds = Diffusion coefficient in the release medium,
T = Diffusion path lengthFor pseudo steady state, the equation can be written as:

$$M = [2D. C_a . C_O (p/T) t]^{1/2} \quad (6)$$

II. MATERIALS

Table 11: List of materials

Sl No.	Ingredients	Company Name
1.	Divalproex sodium	Gift sample from ROAQ Chemicals Pvt. Ltd. Vadodara
2.	Sodium Starch Glycolate	S.D. Fine Chem. Ltd, Mumbai
3.	Croscarmellose	S.D. Fine Chem. Ltd, Mumbai
4.	HPMC K4M	Yarrow Chem Products, Mumbai
5.	HPMC K100M	Yarrow Chem Products, Mumbai
6.	Lactose	S.D. Fine Chem. Ltd, Mumbai
7.	Micro Crystalline Cellulose	S.D. Fine Chem. Ltd, Mumbai
8.	PVP K 30	S.D. Fine Chem. Ltd, Mumbai
9.	Ponceau 4R	Indian fine chemicals, Mumbai-20
10.	Magnesium Stearate	S.D. Fine Chem. Ltd, Mumbai
11.	Talc	S.D. Fine Chem. Ltd, Mumbai

III. PRE-FORMULATION STUDIES

Pre-formulation testing is the first step in rational development of dosage forms of a drug substance. Pre-formulation study is the process of optimizing the delivery of drug throughdetermination of physicochemical properties of the excipients that could affect drug performanceand development of as efficacious, stable and safe dosage form. It provides a framework for the drug combination with pharmaceutical excipients in the dosage form.

Determination of λ^{74}_{max}

Divalproex sodium was dissolved in methanol further diluted with the same and scanned for maximum absorbance in UV

double beam spectrophotometer (Shimadzu 1800) in the range from190 to 380 nm.

Solubility

The solubility of Divalproex sodium was determined in distilled water, methanol, ethanol,acetone, chloroform and pH 6.8 phosphate buffer by shake flask method. An excess amount of Divalproex sodium is added to each vial containing 10 ml of selected solvent till the saturation ofthe solution. The mixtures were subjected to the mechanical agitation for 48 hours in isothermal shaker at $25^0C \pm 1^0C$ followed by filtration through watmann's filter paper. Absorbance is measured by UV-Visible Spectrophotometer. The drug content is calculated by using the standard graph.

Melting point

Melting point of the Divalproex sodium was determined by capillary method in triplicate.

Standard Curve for Divalproex sodium

100 mg of Divalproex sodium was accurately weighted and dissolved in 100 ml of methanol to prepare first stock solution. 10 ml of above solution was taken and diluted to 100 ml with the same solvent to prepare II stock solution. The aliquot amount of II stock solution was further diluted to get 5, 10, 15, 20, 25 and 30 g of drug per ml of the final solution. Then the absorbance was measured in a UV spectrophotometer at 210 nm against methanol blank.

Compatibility studies

The compatibility studies of the drug with polymers are studies using FT-IRspectroscopy.

FT-IR Spectroscopy

FT-IR spectroscopy was carried out to check the compatibility between drug and excipients. Infrared spectroscopy was conducted using s thermo Nicolet FTIR and the spectrum was recorded in the region of 4000 to 400 cm^{-1}. The sample (drug and drug-excipient mixture in 1:1 ratio) in KBr (200-400mg) was compressed in to discs by applying a pressure of 5 tons for 5 min in hydraulic press. The interaction between drug-excipients was observed from IR-spectralstudies by observing any shift in peaks of drug in the spectrum of physical mixture of drug- excipients.

DSC Analysis for formulation

Thermal properties of the pure drug and the physical mixture of drug and excipients were analyzed by Different Scanning Calorimeter -60, Shimadzu limited Japan. The samples were heated in a thermetically sealed aluminium pans. Heat runs for each sample were set from 25 to 350^0C at a heating rate of 10^0C/min, using nitrogen as blanket gas.

IV. FORMULATION DESIGN CALCULATION OF DOSE

The total dose of Divalproex sodium for once daily formulation was calculated by thefollowing equation, using available pharmacological data.

$Dt = Dose\ (1+0.693xt/t1/2)$ Where, Dt = Total dose of drug,

Dose = Dose of immediate release part.

t = time in hr during which the sustained release is desired (18 hrs)$t1/2$ = half life of the drug (9 hrs)

Therefore,

$Dt = 125(1+0.693x18/9)$, $Dt \approx 298.25$

Therefore maintenance dose = 298.25-125 = 173.25 mg.

Hence, the formulation should release 125 mg drug within 1 hour and 173.25 mg drug in 18hours.

V. RESULT AND DISCUSSION

The solubility studies of drug were done by using various media like distilled water, methanol, chloroform and phosphate buffer pH 6.8. The data for solubility studies in those mediaare shown in table 5. The result shows maximum solubility in chloroform.

Table 1: Solubility of Divalproex sodium

Solvents	Solubility (mg/ml)
Distilled water	7.35
Methanol	48.45
Chloroform	55.24
Phosphate buffer pH 6.8	29.73

Result showed that Divalproex sodium is more soluble in chloroform in compare to othersolvents.

Melting Point

Melting point of drug was determined by capillary method. The result is found to be **219**-223^{0}C.

FT-IR spectrum

FT-IR spectrum of pure drug Divalproex sodium and combination of drug with polymers were obtained as shown in figures 6-12. All the characteristic peaks of Divalproex sodium were present in spectrum of drug and polymer mixture, indicating compatibility between drug and polymers. The entire FT-IR spectrum and was tabulated in table 22.

FTIR figure of Drug and Drug with excipients

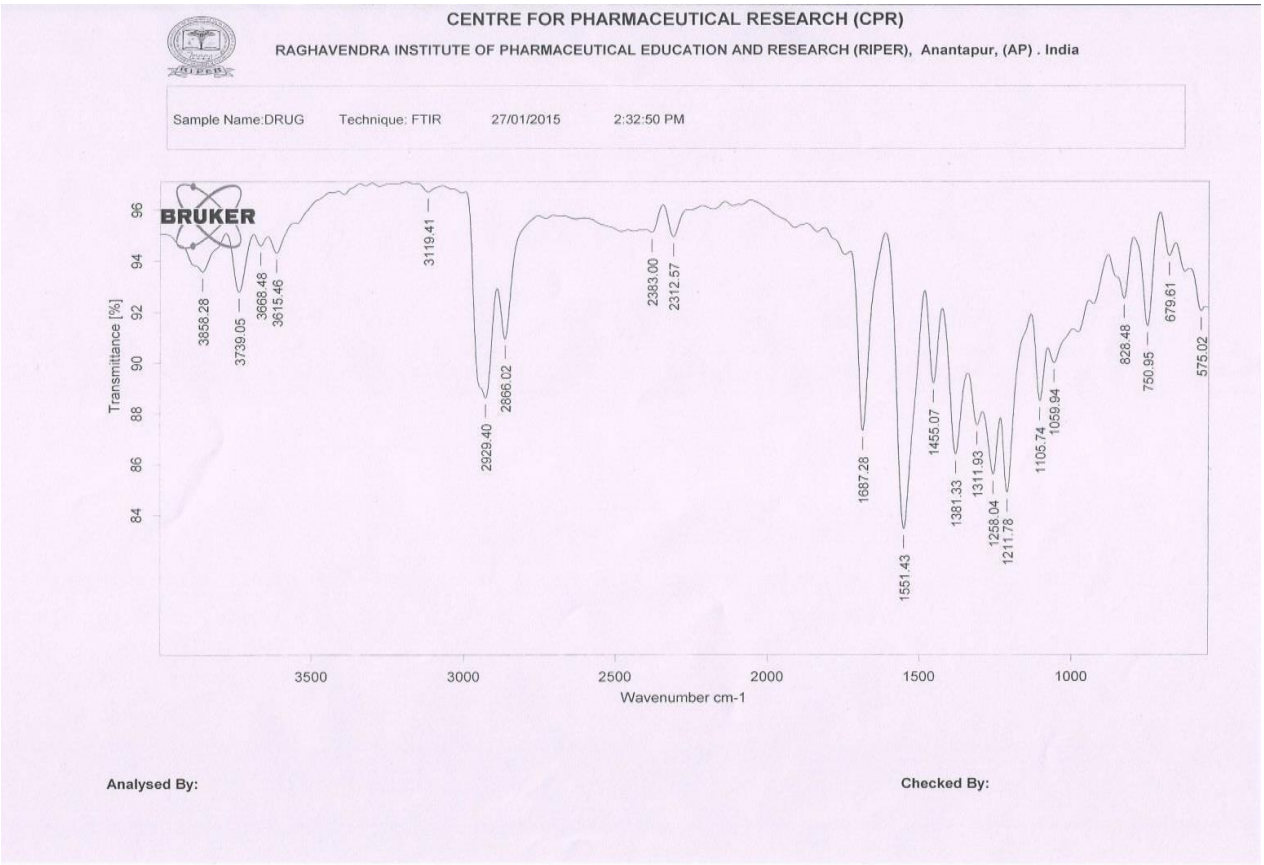

Figure 1: FTIR of Drug Divalproex sodium

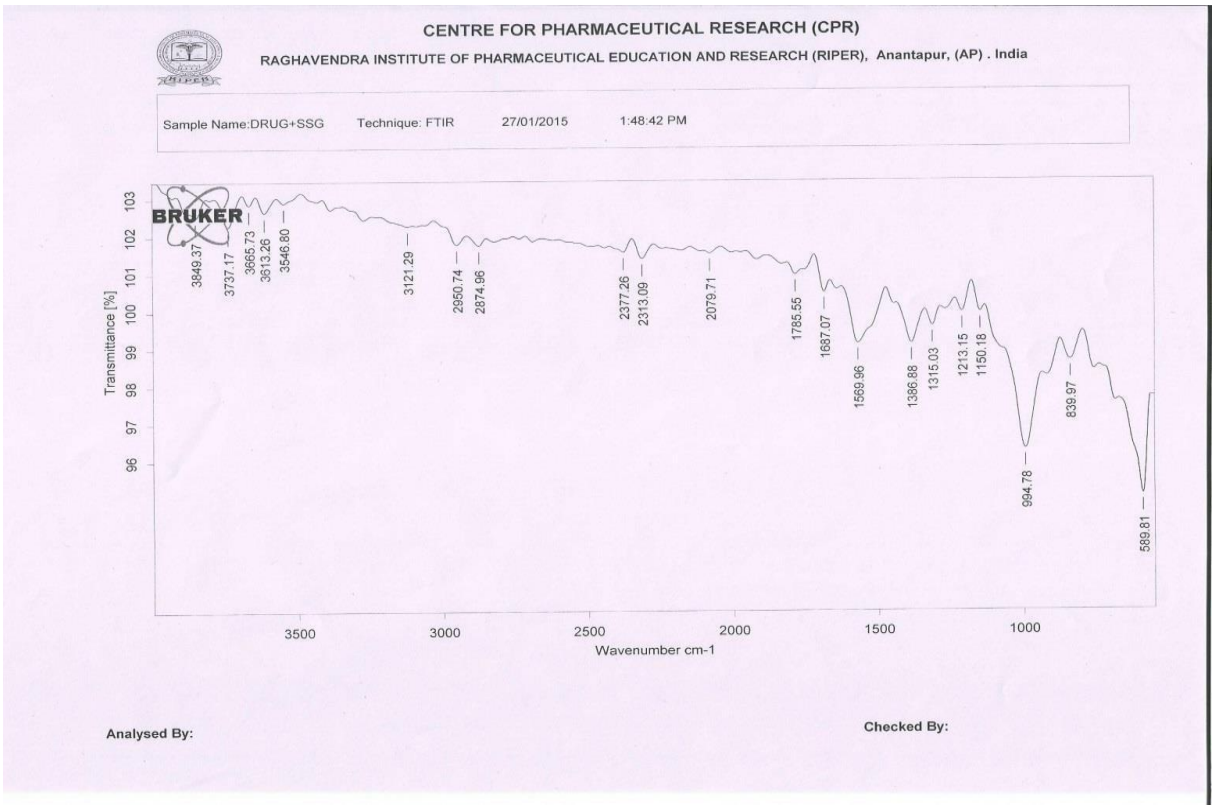

Figure 2: FTIR of Divalproex sodium + Sodium Starch Glycolate (SSG)

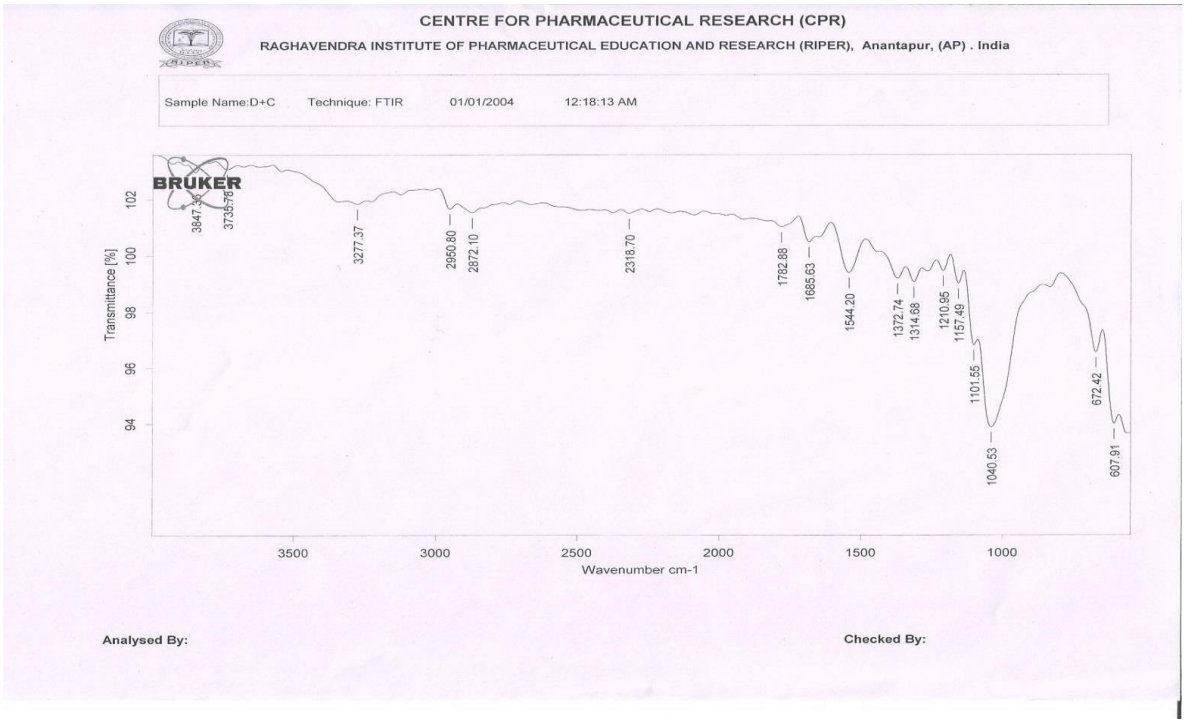

Figure 3: FTIR of Divalproex sodium + Corscarmellose sodium

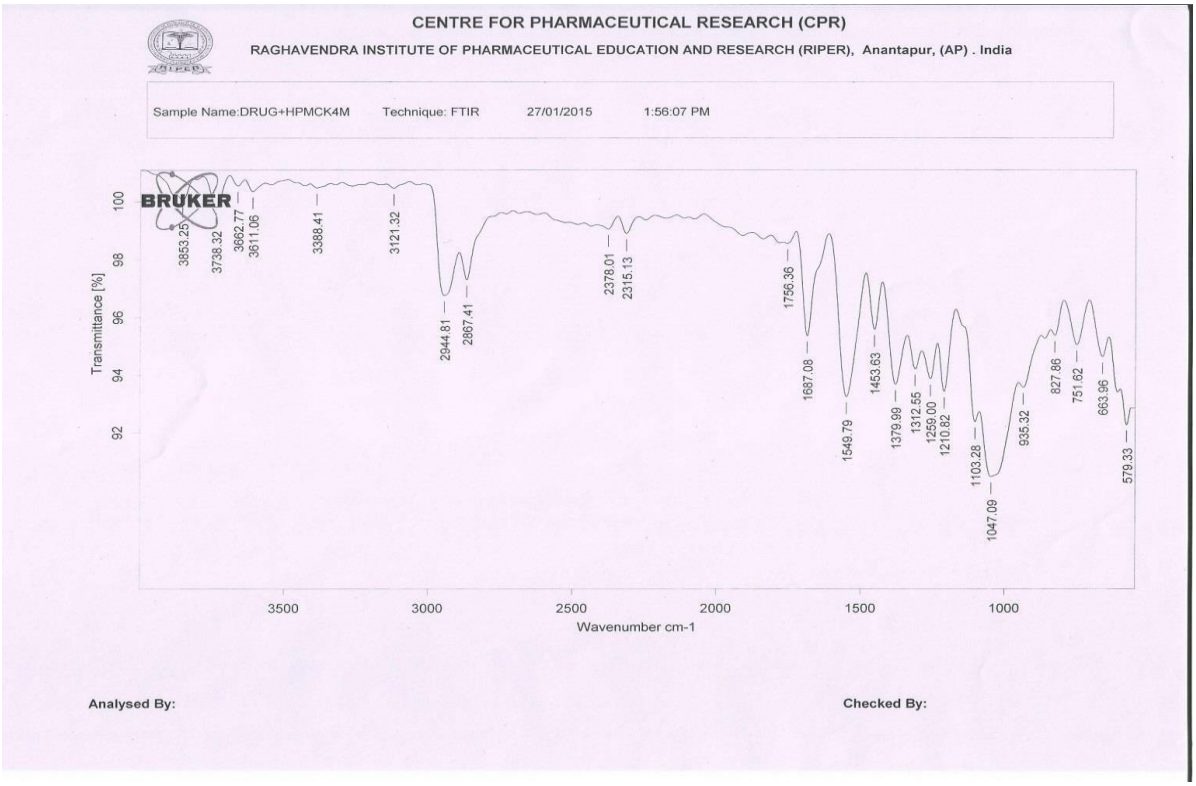

Figure 4: FTIR of Divalproex sodium + HPMC K4M

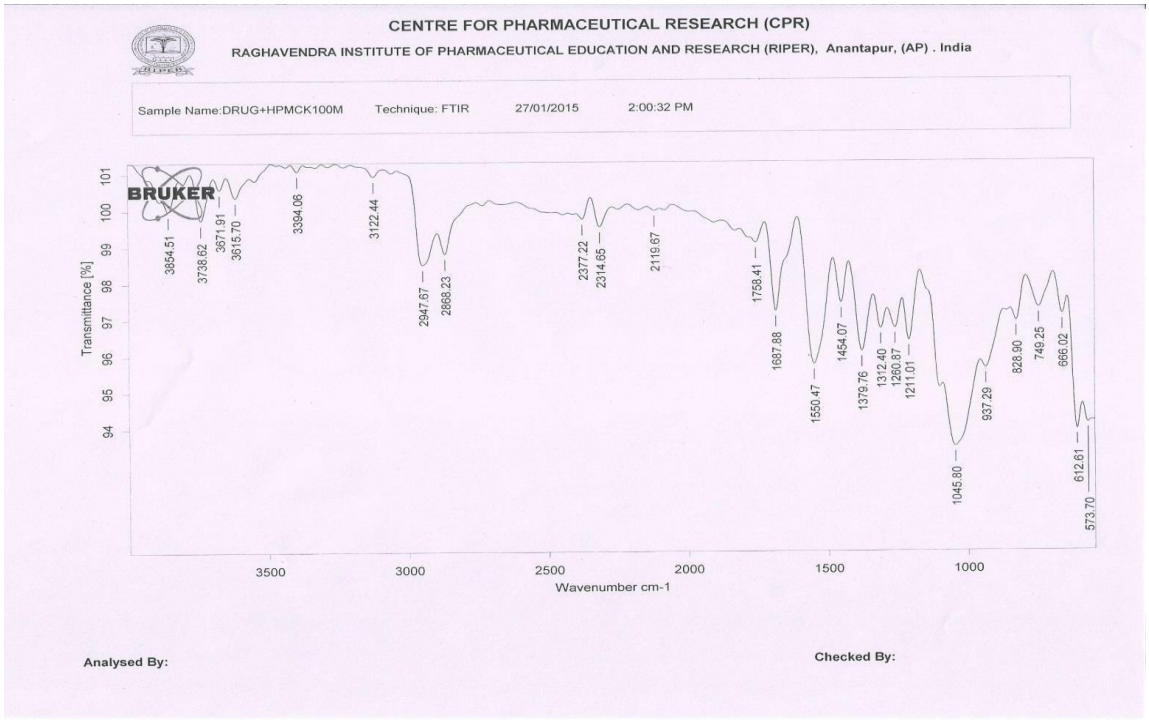

Figure 5: FTIR of Divalproex sodium + HPMC K100M

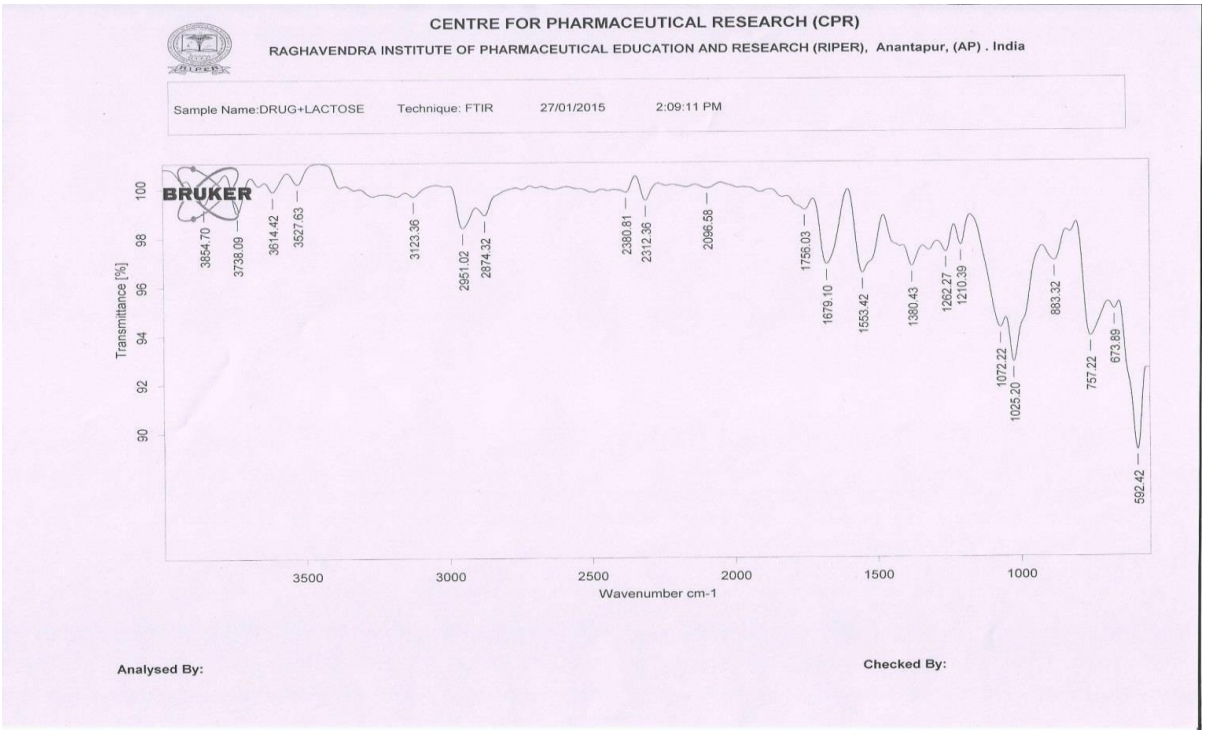

Figure 6: FTIR of Divalproex sodium + Lactose

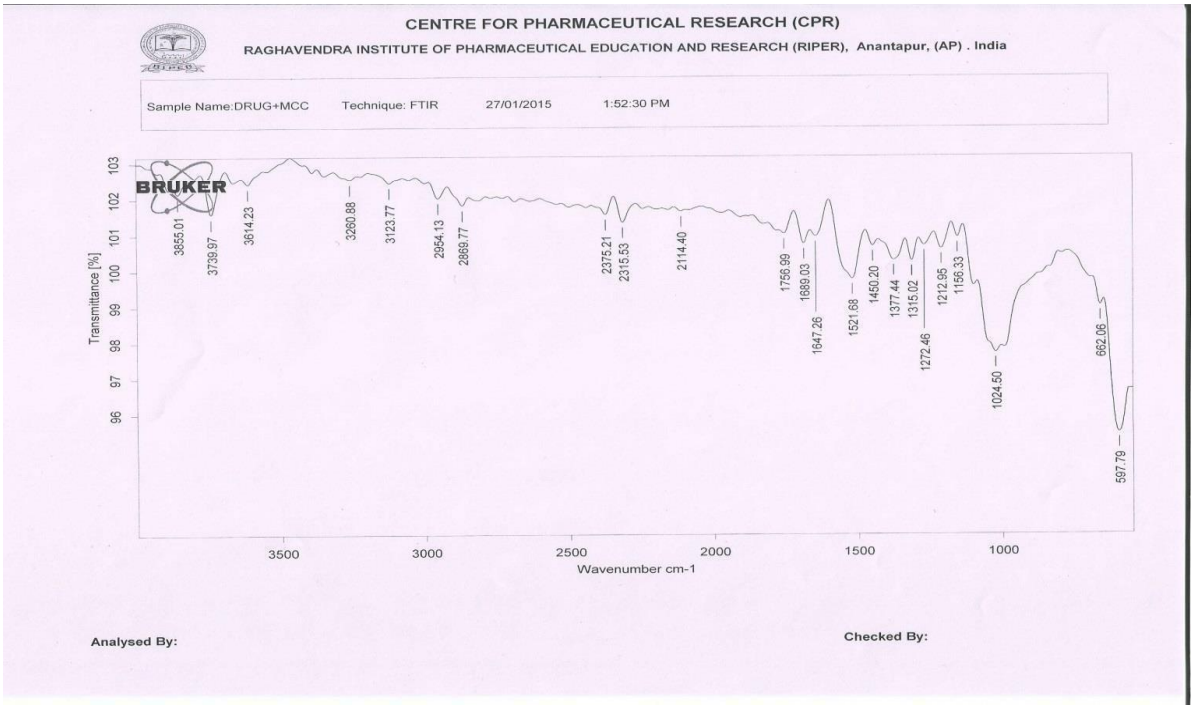

Figure 7: FTIR of Divalproex sodium + Microcrystalline Cellulose (MCC)

VI. CONCLUSION

The above studies lids to following conclusions:

- FTIR and DSC studies indicated that the drug is compatible with all the excipients.
- Both immediate and sustained release layer were prepared by wet granulation method and punched separately. The prepared tablets of both layers were evaluated for post compression parameters.
- According to the *in vitro* dissolution profile date one formulation of each layer were selected for bi-layered tablet. IF6 from immediate release formulations as they showed
  98.62 % drug release within 20 minute. SF8 from sustained release formulation as they showed 94.29 % drug release within 18 hours.
- The bilayer tablets were prepared using the selected immediate and sustained release layer. The prepared tablets were found to be good and free from chipping and capping.
- The hardness of the prepared tablets was found to be in the range of 5.85 to 7.05 kg /cm^2
- The low values of the standard deviation of average weight of the prepared tablets indicate weight uniformity within the batches prepared.
- The friability of the prepared tablet was found to be less than 1%.
- The percentage drug content was uniform in all the formulations of prepared bi-layeredtablets.
- *In vitro* drug release pattern of the bi-layered tablets were same as individual layertablets.
- The stability study showed that no significant changes in tablets after 3 months study.

REFERENCES

1. Notari, R., Biopharmaceutics and Clinical Pharmacokinetics, An Introduction, 3rd Ed., Marcel Dekker Inc. New York, 1980,152-54.
2. Vinay K, Prajapati SK, Girish CS, Mahendra S, Neeraj k. Sustained release matrix type drug delivery system. IRJP 2012;1(3):934-60.
3. Kumar V, Sharma A, Sharma A, Joshi G, Dhillon V. Recent Advances In Novel Drug Delivery System for Delivery Of Anti- Hypertensive Drugs. Int J D D Res.2011;3(1):252-59.
4. Basu B, Bagadiya A, Makwana S, Vipul V, Batt D,Dharamsi A. Formulation and evaluation of fast dissolving tablets of cinnarizine using superdisintegrant blends and subliming material. J Adv Pharm Technol Res. 2011;2(4):266-73.
5. http//www.pharmacopeia.cn/v29240/USP29nf24s0-c115/587.htm/
6. The Indian Pharmacopoeia, Government of India Ministry of health and family welfare, the indian pharmacopoeia commission Ghaziabad, 2014;vol.II:959.
7. Pahade AA, Jadhav VM, Kadam VJ. Formulation and Development of a Bilayer Sustained Released Tablets of Isosorbide Mononitrate. Int J Pharma Bio Sci. 2010;1(4):305-14.
8. Sahoo PK. Phamaceutical Technology,Tablets. New Delhi,2007, P 2-3
9. The Indian Pharmacopoeia, Government of India Ministry of health and family welfare, the indian Pharmacopoeia commission Ghaziabad, 2014; vol II:960-61.
10. Sandeep N. & Gupta M.M, Immediate Drug Release Dosage Form: A review. Journal of Drug Delivery & therapeutics. 2013;3(2):155-61.
11. Pahwa R, Gupta N. A Review: Superdisintegrants in the development of orally disintegratingtablets. Int J Pharm Sci Res. 2011;2(11):2767-2780.
12. Patel U, patel K, Shah D, Shah R. A review on immediate release drug delivery system. Int. j.pharm. Res. Bio-Science. 2012;1(5):37-66.
13. Chugh I, Seth N, Rana A.C. Oral sustained release drug delivery system. International Research Journal of Pharmacy 2012;3(5):57-62.
14. Gennaro AR. (Ed.) Remington's. pharmaceutical science. 20thEdn. Lippincott Williams and wilkini publishing co, Newyork. 2000;1:905-06.
15. Kumar KPS, Bhowmik D, Chiranjib, Chandira M, Tripathi KK. Immovations in Sustained Release Drug Delivery System and Its Market Opportunities. J Chem Pharma Res. 2010;2(1):349-360.
16. Singh A, Sharma R, Jamil F. Sustained Release Drug Delivery System: a Review. Int Res J Pharma.

2012;3(9):21-4.
17. Patel H, Panchal DR, Patel U, Brahmbhatt T, Suthar M. Matrix type drug delivery system: A Review. Journal of Pharmaceutics Science and Bio-scientific Research (JPSBR) 2011;1(3):143-51.
18. Reddy P, Rao D, Kumar RK. Bi-lyaer Technology-An Emerging Trend:A Review. Int J Res Devl Pharma Life Sci. 2013;2(3):404-11.
19. Gopinath C, Bindu VH, Nischala M. An Overview On Bi-layered Tablet Technology. J Glob Trends Pharma Sci. 2013;4(2):1077-85.
20. Jamunadhevi V, Sahoo PK, Kailasam P. Formulation and *in vitro* evaluation of bi-layer tablet of cyclobenzaprine hydrochloride ER and diclofenac potassium IR- A novel fixed dose combination. Int J Res Pharma Sci. 2011;2(2):170-8.
21. Kumar AH, Kavitha K, Kumar SAK, Kumar MR, Singh SDJ. Novel Approch of Bilayer Tablet Technology-A Review. Int J Pharma Chem Bio Sci. 2013;3(3):887-93.
22. Debnath M. Bilayer Tableting Technology:An Overview. J Pharma Res. 2012;5(1):310-4.
23. Divya A, Kavitha K, Kumar MR, Dakshayani S, Singh SDJ. Bilayer tablet technology:An overview. J Applied Pharma Sci. 2011;)1(08):43-7.
24. http://en.wikipedia.org/wiki/central_nervous_system_disease.
25. http://www.sabiosciences.com/CNS_Disorders.php.
26. Sridharan R. Epidemiology of epilepsy. Current Sciences. 2002;82(6):664-70.
27. Goodman and Gillman's the Pharmaceutical Basic of Therapeutics-11th ed.2006, McGraw-Hill, Medical Publishing Division.
28. Lippincott Williams & Wilkons, Lippincott's illustrated Reviews: Pharmacology. 4th edition; wolter Kluwer.