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An investigation on effect of various hydrophobic polymers alone and in combination with hydrophilic polymers on matrix tablets of desvenlafaxine succinate

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ABSTRACT

This work aims at investigating the effects of different hydrophobic polymers alone and in combination with hydrophilic polymers on *in vitro* drug release in an attempt to formulate matrix tablets of desvenlafaxine succinate. Matrix tablets were prepared by wet granulation method employing different types and levels of polymers viz. Eudragit RS-100, Eudragit S-100, Eudragit L-100 and hydroxypropyl methylcellulose (HPMC) K15M. The granules were evaluated for angle of repose, density, compressibility index and Hausner's factor showed satisfactory results. Compressed tablets were evaluated for thickness, friability, hardness, uniformity of weight, content of active ingredient, swelling and *in vitro* dissolution studies. FT-IR spectra revealed that there was no interaction between drug and polymers. All the formulations showed compliance with pharmacopoeial standards. It was observed that combination of both hydrophilic and hydrophobic polymers in equal concentration exhibited the best release profile compared to be used alone and able to sustain the drug release for 10 h. The studies indicated that the drug release can be modulated by varying concentrations and types of polymers. The formulations were subjected to stability studies at different temperature and humidity conditions as per ICH guidelines. Combination of polymer undergoes swelling as well as erosion during the dissolution study, which indicates that polymer relaxation had a role in drug release mechanism. The release data were fitted to various mathematical models such as Higuchi, Korsmeyer-Peppas, first-order and zero-order to evaluate the release kinetics and mechanism of the drug release found to be diffusion coupled with erosion.

Keywords: Desvenlafaxine Succinate; Eudragit; Hydroxypropyl Methylcellulose; Matrix Tablets; Sustained/ Controlled release.

polymer excipient for retarding *in vitro* drug release (Manavadaria KG et al, 2012). Therefore, in this study an attempt was made to obtain more sustained drug release profile for water soluble drug DVS using hydrophobic polymers and its combination with hydrophilic polymers to allow the formulator the flexibility in tailoring the convenient drug release. In a long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages (Chien YW, 2007). The reduced side effects and lower frequency of administration of extended release (ER) tablets represents increased comfort and improved patient compliance and more

ty, ease in manufacturing, high level of reproducibility, stability of the raw materials and dosage form, ease of scale-up and process validation. This is reflected by the large number of patents filed each year and by the commercial success of a number of novel drug delivery systems based on matrix technologies (Verma MVS et al, 2004). More recently, hydrophobic polymers, such as acrylic resins, have been used for the preparation of controlled release formulations since they possess some very interesting characteristics, i.e. excellent flow properties and weight uniformity. Drug content uniformity has also been observed with tablet formulations (Al-Hmoud H et al, 1991). A new focus has been directed towards investigating the use of polymer blends of pharmaceutically approved polymeric materials as matrix excipients to retard drug release (Ebube NK et al, 2004). A serotonin-norepinephrine reuptake inhibitor (SNRI), desvenlafaxine succinate (DVS) for the treatment of adult patients with major depressive disorder (MDD). After oral administration, desvenlafaxine reaches t_{max} in 7 to 8 h and is slowly eliminated, with

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Table 1: Composition of desvenlafaxine succinate matrix tablets prepared by hydrophobic and combination of hydrophilic and hydrophobic polymers

Ingredients	Formulation code											
	ERS4	ERS6	ERS8	ES4	ES6	ES8	EL4	EL6	EL8	E2H6	E6H2	E4H4
DVS	50	50	50	50	50	50	50	50	50	50	50	50
Eudragit RS-100	40	60	80	-	-	-	-	-	-	20	60	40
Eudragit S-100	-	-	-	40	60	80	-	-	-	-	-	-
Eudragit L-100	-	-	-	-	-	-	40	60	80	-	-	-
HPMC K15M	-	-	-	-	-	-	-	-	-	60	20	40
Lactose	106	86	66	106	86	66	106	86	66	66	66	66
Isopropyl Alcohol	-	-	-	-	-	-	-	-	-	q.s.	q.s.	q.s.
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Total Weight	200	200	200	200	200	200	200	200	200	200	200	200

*All quantities are in mg. q.s. indicates quantity sufficient

$t_{1/2}$ values of 9 to 15 h (Richard P et al, 2009). With once daily dosing, steady state plasma concentrations are achieved within 4 to 5 days. Therefore, development of sustained release dosage form of desvenlafaxine in the form of tablets to be taken once daily is necessary.

Therefore, this work aims at investigating different types and levels of hydrophobic matrixing agents, including eudragit RS-100, eudragit S-100 and eudragit L-100 alone and in combination with HPMC K15M in an attempt to formulate sustained release matrix tablets containing 50 mg desvenlafaxine succinate and to investigate how polymer characteristics may influence drug release from these systems.

MATERIALS AND METHODS

Materials

Desvenlafaxine succinate was procured from Ami Life Sciences (Baroda, India). Eudragit RS-100, Eudragit S-100, Eudragit L-100 and HPMC K15M were procured from Yarrow Chem. Products, Mumbai. Isopropyl alcohol, lactose, magnesium stearate and talc were obtained from Lobachemie, Mumbai.

Methods

Drug-excipients interaction

This was carried out to find out the compatibility between the drug (DVS) and the polymers such as Eudragit RS-100, Eudragit S-100, Eudragit L-100, HPMC K15M. 10 mg of sample and 400 mg of potassium bromide were taken and triturated. A small amount of the triturated sample was taken into a pellet making disc and was compressed using a hydraulic press. The pellet was kept onto the sample holder and scanned from 4000 cm^{-1} to 400 cm^{-1} in FT-IR spectrophotometer (Alpha, Bruker). Samples were prepared for drug desvenlafaxine and the physical mixtures of drug and polymers. The spectra obtained were compared and interpreted for the functional group peaks.

Different matrix tablet formulations as described in Table 1 were prepared by wet granulation technique using various polymers. All the powders were passed through B.S.S. sieve No. 60 and deagglomerated. Required quantities of drug, polymer and diluents were mixed thoroughly, and a sufficient volume of granulating agent (isopropyl alcohol and/or water) was added slowly. After enough cohesiveness was obtained, the mass was sieved through B.S.S. sieve no. 12, dried at 60 °C for 1 h. Once dried, the granules were again sieved through sieve No. 16/44 to obtain almost uniform sized granules. The granules retained on sieve No. 44 were mixed with 15% of fines (granules that passed through sieve No. 44). Talc and magnesium stearate (1% w/w of dried granules) were finally added as glidant and lubricant (Abdelkader H et al, 2007). The granules were compressed into tablets using hydraulic 10 station rotary tablet press machine (Rimekminipress I, Karnavati, Ahmedabad) equipped with flat faced punches of 8 mm diameter. All the tablets were weighed 200 mg containing 50 mg of DVS.

Evaluation of granules

Angle of Repose

The angle of repose of granules was determined by the funnel method (Mutalik S et al, 2003). The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation (Cooper J et al, 1986).

$$\tan \theta = h/r$$

Where 'h' and 'r' are the height and radius of the powder cone respectively.

Table 2: Physical properties of desvenlafaxine succinate granules

Formulation Code	Angle of Repose (°)	Bulk density (g/cm ³)	Tapped density (g/cm ³)	Hausner Factor	Carr's Index (%)
ERS4	25.70	0.435	0.496	1.141	12.35
ERS6	25.38	0.443	0.503	1.134	11.85
ERS8	24.37	0.528	0.577	1.093	08.51
ES4	24.98	0.467	0.523	1.120	10.71
ES6	26.82	0.479	0.583	1.217	17.83
ES8	25.23	0.502	0.564	1.124	11.05
EL4	24.63	0.523	0.594	1.137	12.07
EL6	23.99	0.498	0.563	1.130	11.54
EL8	24.45	0.472	0.545	1.153	13.32
E2H6	26.45	0.466	0.547	1.173	14.77
E6H2	25.99	0.450	0.513	1.138	12.20
E4H4	25.28	0.425	0.488	1.146	12.74

Bulk Densities

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined (Mutalik S et al, 2003). A weighed quantity of granules from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formula (Banker GS et al, 2008).

$$\text{LBD} = \frac{\text{Weight of the powder}}{\text{Bulk volume of the packing}}$$

$$\text{TBD} = \frac{\text{Weight of the powder}}{\text{Tapped volume of the packing}}$$

Carr's Compressibility Index

Carr's index is a one-point determination and does not always reflect the ease or speed with which the powder consolidates. The compressibility index of the granules was determined by Carr's compressibility index (Aulton ME et al, 2002).

$$\text{Carr's index (\%)} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100$$

Hausner's Factor

Hausner found that the ratio TBD/LBD was related to interparticle friction and as such, could be used to predict powder flow properties (Banker GS et al, 2008).

$$\text{Hausner's factor (H.F.)} = \frac{\text{TBD}}{\text{LBD}}$$

Evaluation of Tablets**Thickness**

The thickness of the tablets was determined using thickness screw gauge. Five tablets from each batch were randomly selected, evaluated and their values were reported in millimeters. The average mean and SD were calculated (Mutalik S et al, 2003).

Weight Variation Test

To study weight variation, randomly selected 20 tablets from each formulation were weighed individually using an electronic balance (AR2130, Ohaus Corp.) and the test was performed according to the official method (Indian Pharmacopoeia, 2010). The percentage deviation from average weight was reported.

Hardness

For each formulation, the hardness of six randomly selected tablets was determined by Monsanto hardness tester (Campbell electronics). The force of fracture is recorded and values were reported in Kg/cm². The average mean and SD were calculated (Banker GS et al, 2008).

Friability

Six tablets from each formulation were randomly selected, weighed together and then placed in the friabilator chamber (Campbell electronics). The friabilator was operated for 100 revolutions at 25 rpm. The tablets were then dedusted and re-weighed. The friability was calculated as the percentage weight loss (Banker GS et al, 2008).

$$\% \text{ Friability} = \frac{[(\text{Initial weight} - \text{Final weight}) / \text{Initial weight}] \times 100}$$

Drug Content Estimation

Five tablets were weighed individually, then placed in a mortar and powdered with a pestle. An amount equivalent to 50 mg drug was extracted with 100 ml of phosphate buffer pH 6.8. The solution was filtered through a filter paper (Whatmann 0.22-μm pore size), properly diluted with phosphate buffer pH 6.8 and then absorbance was measured at 224 nm using UV spectrophotometer (UV1800, Shimadzu) and the percentage of drug content was calculated (Ranjitkumar P et al, 2010).

Table 3: Evaluation of matrix tablets of desvenlafaxine succinate

Formulation Code	Thickness* (mm)	Hardness** (kg/cm ²)	Friability (%)	% Weight Variation [^]	% Drug Content*
ERS4	2.380±0.041	5.96±0.23	0.38	2.712±1.84	98.18±0.58
ERS6	2.510±0.072	5.80±0.16	0.38	1.898±1.40	99.57±0.98
ERS8	2.664±0.078	5.75±0.10	0.40	2.960±1.38	98.45±0.45
ES4	2.440±0.094	5.90±0.21	0.43	2.463±1.64	99.44±0.52
ES6	2.534±0.075	6.09±0.14	0.43	2.439±1.63	98.43±0.78
ES8	2.758±0.067	6.11±0.20	0.42	2.616±1.70	100.08±0.48
EL4	2.340±0.060	5.90±0.07	0.48	2.569±1.87	97.74±0.69
EL6	2.426±0.088	5.86±0.13	0.50	2.394±1.93	100.44±0.64
EL8	2.564±0.054	5.80±0.10	0.50	2.582±1.70	100.55±1.05
E2H6	2.886±0.052	5.66±0.18	0.49	1.632±1.72	99.00±0.65
E6H2	2.652±0.105	5.83±0.14	0.46	1.788±1.35	97.77±0.92
E4H4	2.680±0.107	5.75±0.15	0.47	1.980±1.82	99.52±0.43

*All values expressed in mean ± SD, n=5 ** All values expressed in mean ± SD, n=6

[^] All values expressed in mean ± SD, n=20

Swelling and Erosion Studies

Swelling experiments were conducted on the prepared tablets using USP dissolution apparatus II at rotational speed of 50 rpm at 37 °C as per method described by Al-taaniet *al*(Al-taani BM *et al.*, 2003). The medium used was 900 ml of phosphate buffer pH 6.8. The percentage of swelling and erosion were calculated according to the following formula.

$$\% \text{ Swelling} = S/R \times 100$$

S= weight of the matrix after swelling

$$\% \text{ Erosion} = (T-R)/T \times 100$$

R=weight of the eroded matrix

T=initial weight of the matrix

In Vitro Drug Release Studies

In vitro drug release studies were carried out by using USP Dissolution Apparatus II (Paddle type) [Electro-labTDT-08L] at 50 rpm. The drug release profile was studied in 900 ml of phosphate buffer pH 6.8 by maintaining at 37 ± 0.5 °C. Aliquots of 5 ml of dissolution medium were withdrawn at specific time intervals, filtered and replaced with another 5 ml of fresh dissolution medium. The amount of drug released was determined by UV spectrophotometer (UV1800, Shimadzu) at 224 nm. The release studies were conducted in triplicate and the mean values were plotted versus time with SDs of less than 3, indicating the reproducibility of the results.

Drug Release Kinetics

The kinetics of drug release from formulations was determined by finding the best fit of the dissolution data (drug-released fraction vs. time) to distinct models: zero-order, first-order and Higuchi (Higuchi T *et al.*, 1963). To better characterize the drug release behavior for the polymeric systems studied, namely to under-

stand the corresponding mechanism, the Korsmeyer–Peppas semi-empirical model was applied (Korsmeyer RW *et al.*, 1983).

$$Q_t/Q_\infty = k \cdot t^n$$

Where, Q_t/Q_∞ is the fraction of drug released at time t ; k is a constant comprising the structural and geometric characteristics of the tablet. In addition, for determination of the exponent n , one must use only the initial portion of the curve ($Q_t/Q_\infty < 0.6$) (Peppas NA, 1985; Peppas NA *et al.*, 1989). The release exponent n is a parameter which depends on the release mechanism and is thus used to characterize. For the case of cylindrical tablets, in particular, $n = 0.45$ corresponds to a Fickian diffusion release (case I diffusional) and non-Fickian (anomalous) release, coupled diffusion and polymer matrix relaxation occurs if $0.45 < n < 0.89$, purely matrix relaxation or erosion-mediated release occurs for $n = 0.89$ (zero order kinetics) and super case II type of release occurs for $n > 0.89$. The release exponent, ' n ' is the slope of log fraction of drug release vs log time curve.

Stability studies

The optimized formulation was subjected to stability studies as per ICH guidelines at 40 ± 2 °C and 75 ± 5 % RH in a stability chamber (LPC-170G, Labtop Instruments) for a period of six months and at room temperature (25 ± 2 °C) in a desiccator. After each month tablet sample was analyzed for physical characteristics and percentage drug content.

The selected drug passed the various tests of identification and analysis. The pure drug (Desvenlafaxine succinate) and the solid admixture of drug and various polymers used in the preparation of matrix tablet formulations were characterized by FTIR spectroscopy to know the compatibility (Fig. 1-5). Granules of the different formulations were evaluated for angle of re-

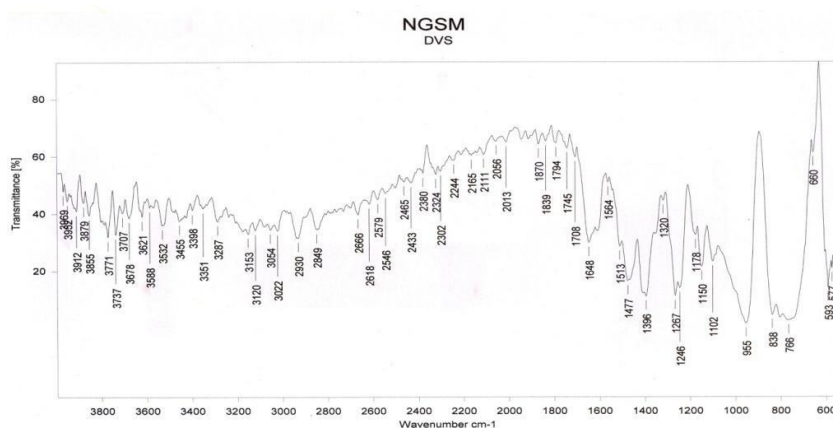


Figure 1: FT-IR spectra of DVS

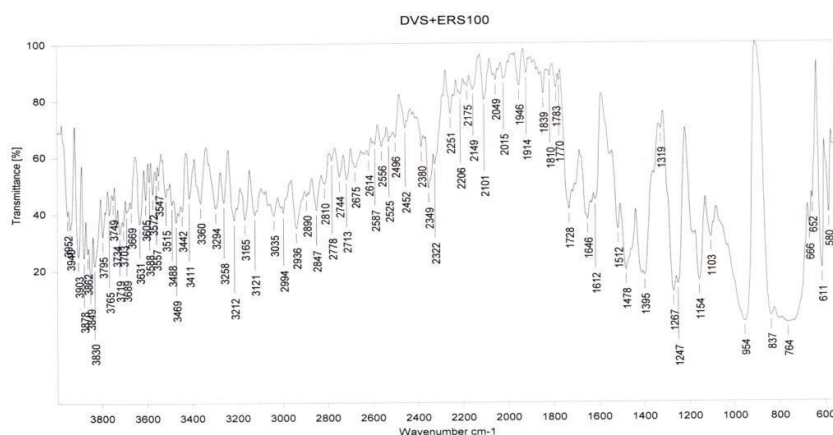


Figure 2: FT-IR spectra of DVS admixed with Eudragit RS-100

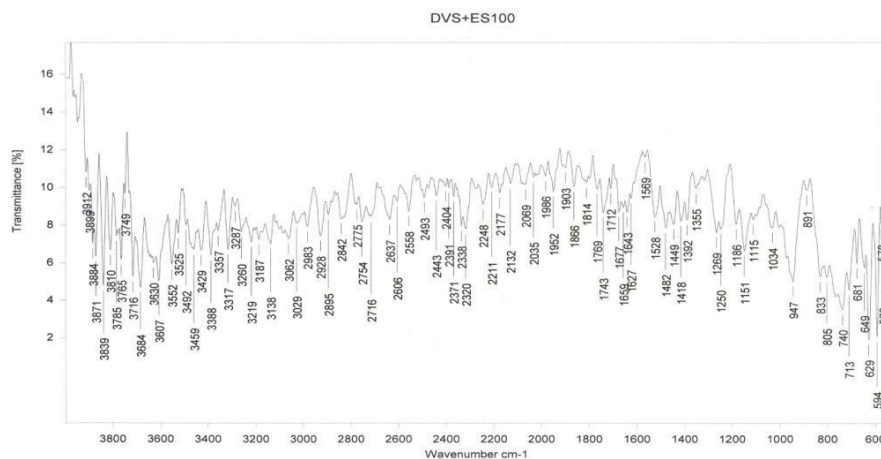


Figure 3: FT-IR spectra of DVS admixed with Eudragit S-100

pose, loose bulk density, tapped bulk density, compressibility index and Hausner factor.

The results of angle of repose and compressibility index (%) ranged from 23.99° to 26.82° and 8.51 to 17.83, respectively in Table 2. The results of loose bulk density and tapped bulk density ranged from 0.425 to 0.528 and 0.488 to 0.594 respectively. The results of angle of repose (<30°) indicate good flow properties of granules (Aulton ME et al, 2002). This was further supported by lower compressibility index values. Further, compressibility index values upto 20% result in good to

excellent flowability and compressibility (Aulton ME et al, 2002; Michael EA, 2002). HF values ranged from 1.093 to 1.217. Hausner showed that granules with low interparticle friction had ratios of approximately 1.2 compared to powders. This indicates good flow properties of the prepared granules as a result of increasing particle size owing to granulation eliminating cohesiveness (Michael EA, 2002). Also granules prepared with hydrophobic polymers showed lower angle of repose compared to hydrophilic polymers. The physical properties of different batches of developed matrix tablets are given in Table 3. The thickness of the prepared tab-

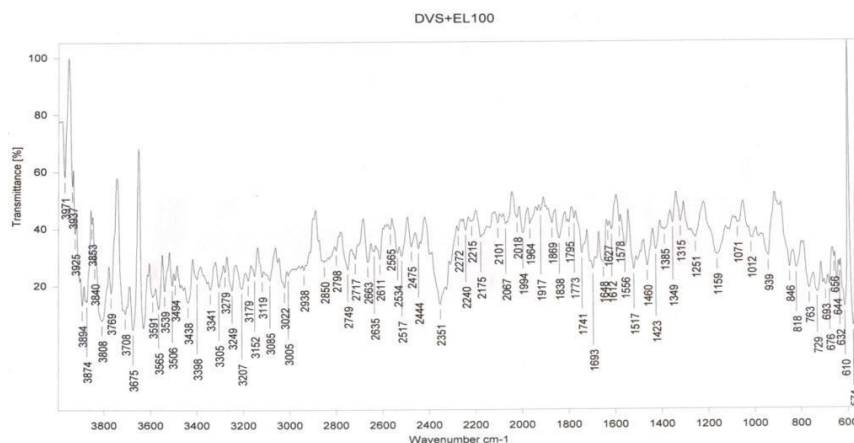


Figure 4: FT-IR spectra of DVS admixed with Eudragit L-100

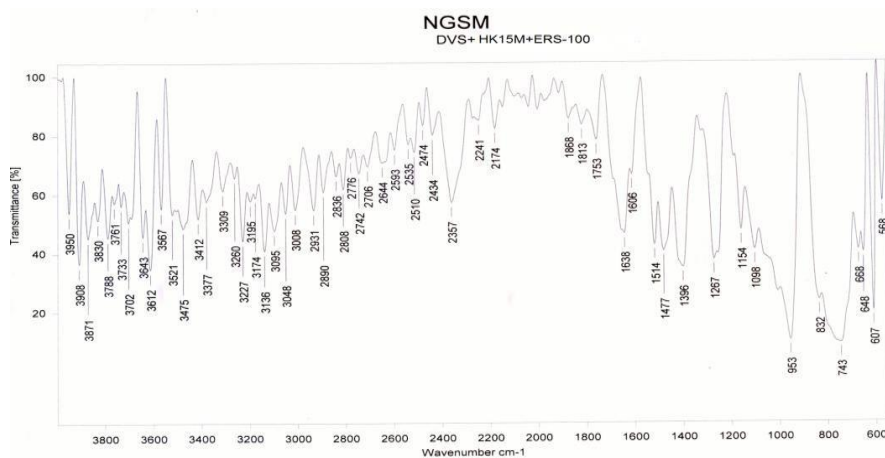


Figure 5: FT-IR spectra of DVS admixed with HPMC K15M and ERS-100

lets was uniform and ranged from 2.340 ± 0.060 mm to 2.886 ± 0.052 mm. Also, it was observed that increasing polymer concentrations resulted in a slight increase in the thickness of the tablet. These results might indicate that the polymers had low binding properties (Abdelkader H et al, 2007).

The average percentage deviation of 20 tablets of each formulation was less than (± 7.5 %), and hence all formulations passed the test for uniformity of weight. Hardness of the tablets fell into the range of 5.66 ± 0.18 kg/cm² to 6.11 ± 0.20 kg/cm². These results were in good agreement with those of thickness and friability. Tablet hardness is not an absolute indicator of strength (Banker GS et al, 2008). Friability of each formulation ranged from 0.38% to 0.50% indicating that the friability is within the prescribed limit of 1% according to European and US pharmacopoeia. The values of percentage drug content were found to be uniform and ranged from 97.74 ± 0.69 % to 100.55 ± 1.05 %. It was found that the drug content was more uniform in formulations containing hydrophobic polymers due to their good flow properties. The percentage swelling and erosion of formulation E4H4 prepared with equal proportion of HPMC K15M and Eudragit RS-100 at the end of 7 h was found to be 236.34 % and 62.57 % respectively (Fig 6). From this study, it was concluded

that matrix tablet undergo swelling as well as erosion during the dissolution study which indicates that polymer relaxation had a role in drug release mechanism. This may occur due to the presence of both hydrophilic and hydrophobic polymers which allows little swelling but did not allow rapid diffusion of the drug from the matrix. The results of *in vitro* drug release studies of matrix tablets of DVS prepared by different formulations are shown in Fig no. 7 and Fig no. 8. A perusal of Fig no. 7, it can be seen that formulations ERS4, ERS6 and ERS8 loaded with 20%, 30% and 40% of the ERS100 (pH-independent polymer) released ~90% of the drug over 3.5, 5.5 and 8.5 h respectively. Whereas formulations loaded with 40% of the ES100 (pH-dependent) and EL100 (pH-dependent) released ~90% of the drug within 6.5 and 5.5 h respectively. These results might be explained on the basis that as the polymer content increased, the drug release rate decreased due to decreasing the total porosity of the matrices (initial porosity plus porosity due to the dissolution of the drug) and increasing tortuosity (the length of the diffusion path of the solute) (Reza MS et al, 2003).

Also, dissolution and erosion rates of EL100, pH-dependent solubility polymer was markedly higher in dissolution medium of phosphate buffer pH 6.8. Drug particles present in the surface of the matrix were

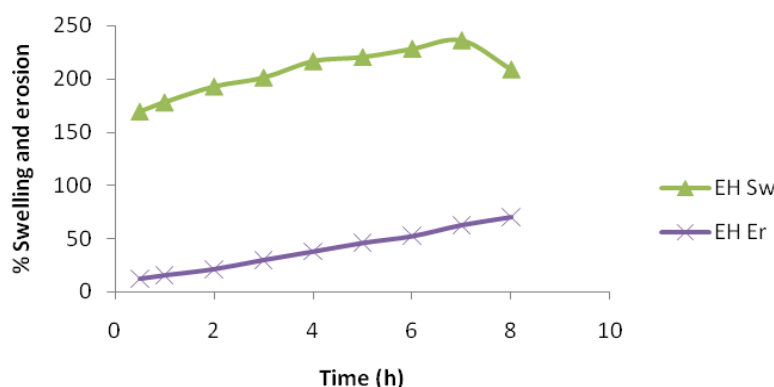


Figure 6: Percentage swelling and erosion of E4H4

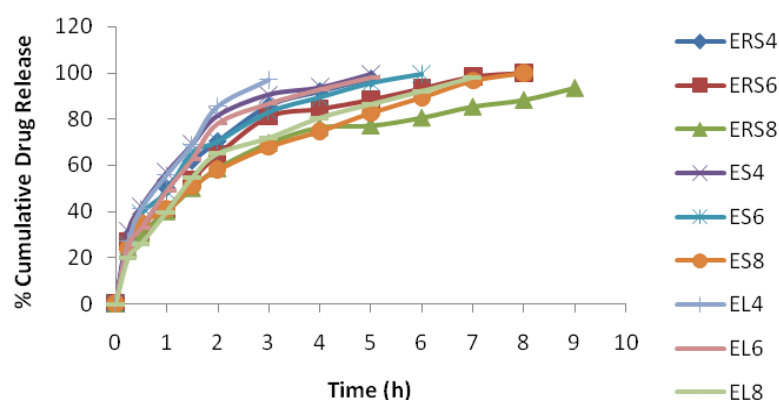


Figure 7: In vitro drug release profile of DVS from various eudragit matrices

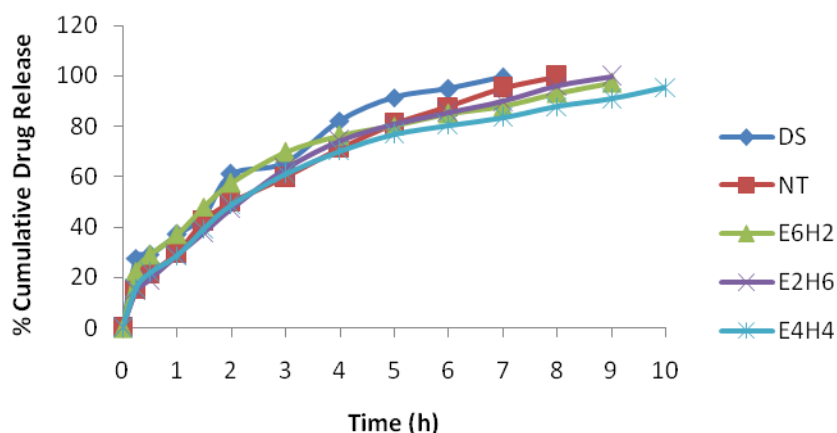


Figure 8: In vitro drug release profile of DVS from different HPMC matrices

initially released into surrounding media generating many pores and cracks which facilitates further release of the drug. Irrespective of polymer nature, as the polymer content increased, the release rate significantly decreased, suggesting that the matrix with higher polymer content provides a more tortuous pathway, and/or a less porous tablet was formed. A perusal of Fig no. 8, ERS being a hydrophobic polymer could lower the water penetration and provide effective release retardation when used in combination with a hydrophilic polymer such as HPMC in matrix. The formulation with ratio 1:1 of E-RS100 and HPMC K15M (E4H4) provided the desired 10 h sustained release profile. Thus E-RS lowered the amount of HPMC K15M required when used in matrix combination. The above

data was compared with marketed formulations where ~90% of the drug released from DS and NT within 5 and 6.5 h respectively. The above data clearly indicate that the drug release can be effectively controlled by varying the polymer and its ratio.

To know the mechanism of drug release from these formulations, the data were treated according to first order, Higuchi's and Korsmeyer equations along with zero order pattern. All the prepared formulations showed first order drug release with regression coefficient ranged from 0.7 to 0.9836. To evaluate drug release mechanism from the matrix tablets, plots of cumulative percentage release vs square root of time as per Higuchi's equation were constructed. These plots were found to be linear (R^2 : 0.9642 to 0.9970)

with all the formulations. To confirm the diffusion mechanism, the data were fit into Korsmeyer et al's equation. The formulations showed good linearity (R^2 : 0.8710 to 0.9903) with slope (n) values ranging from 0.36 to 0.55 indicating that the diffusion is the dominant mechanism of drug release with these formulations. Most of this n value, however, appears to indicate a coupling of diffusion and erosion mechanisms so called anomalous (non-fickian) diffusion.

CONCLUSION

The matrix tablets were found to be effective in sustaining the drug release upto 10 h prepared with equal proportion of HPMC K15M and Eudragit RS-100 polymers and found that concentration of polymer had significant effect on drug release. Drug release was found to be diffusion coupled with erosion with first order kinetics. Stability studies revealed that there was no significant change in drug content of matrix tablets. FTIR studies revealed that there was no shift in peaks, indicating there is no interaction between DVS and other ingredients used. It can be concluded that stable formulation could be developed by incorporating various hydrophilic and hydrophobic polymers in a definite proportion. So that the sustained released profile is maintained for an extended period of time.

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