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Hybrid polymeric matrices for oral modified release Desvenlafaxine succinate tablets

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ABSTRACT:

PURPOSE: Desvenlafaxine succinate (DSV) is a water soluble anti-depressant drug, which is rapidly absorbed after oral administration exaggerating its side effects. The current work aims to prepare controllable release DSV matrix to reduce DSV side effects related to its initial burst. *METHODS*: Fifteen DSV matrix formulations were prepared using different polymers, polymer/drug ratios and matrix excipients and characterized using Differential Scanning Calorimetry (DSC), infra-red (IR) spectroscopy, water uptake and *in-vitro* DSV release. The release kinetics were calculated to determine the drug release mechanism. *Ex-vivo* DSV absorption via rat intestinal mucosal cells and the calculation of the apparent permeability coefficient (P_{app}) were performed using everted sac technique. *RESULTS:* Maltodextrin was the best matrix excipient (F7 and F10) showing acceptable decrease in the initial burst compared to the innovator. The addition of negatively charged polymers sodium carboxy methyl cellulose (SCMC) or sodium alginate resulted in an interaction that was proved by DSC and IR findings. This interaction slowed DSV release. F10 showed an excellent absorption of more than 80% of DSV after 4 hours and the highest similarity factor with the innovator (84.7). *CONCLUSION:* A controllable release pattern of DSV was achieved using Methocel, Maltodextrin and SCMC. The obtained results could be used as a platform to control the release of cationic water soluble drugs that suffer from side effects associated with their initial burst after oral administration.

KEYWORDS: Desvenlafaxine succinate; controlled release matrix; apparent permeability coefficient; everted sac.

ABBREVIATIONS: P_{app}, apparent permeability coefficient; DSV, desvenlafaxine succinate; DSC, differential scanning calorimetry; FDA, Food and Drug Administration; HPMC, hydroxyl propyl methyl cellulose; IR, infra-red; SF, similarity factor; SA, sodium alginate; SCMC, sodium carboxy methyl cellulose.

1. INTRODUCTION

Desvenlafaxine (DSV) is the major active metabolite of the third generation anti-depressant, venlafaxine (Pae et al., 2009). DSV is comparable to venlafaxine in efficacy; but elicits lesser side effects (Coleman et al., 2012). DSV was approved by the Food and Drug Administration (FDA) in 2008 for use in major depressive disorder (Perry and Cassagnol, 2009). It is also used in neuropathic pain, menopause vasomotor symptoms and anxiety (Pae et al., 2009).

DSV, being a weak basic drug (Völgyi et al., 2010), dissolves easily in gastric fluids and is highly absorbed after oral administration, which exaggerates its side effects. Indeed, this highlights the need to prepare extended release DSV tablets to increase the compliance of patients suffering from depressive disorder and decrease side effects compared to the immediate release formulation (Franek et al., 2015; McLaughlin et al., 2007). Being a relatively new drug (Hussar and Campoli, 2008); few trails have been made to develop sustained release preparation of DSV. For instance, in 2015, Payghan and co-workers prepared DSV controlled release matrix tablet by melt granulation technique using chemically inert lipids such as Compritol 888 ATO, Precirol ATO 5 and hydrogenated castor oil.

Combinations of hydroxypropyl methylcellulose (HPMC) and sodium carboxymethyl cellulose (SCMC) have been utilized to minimize the release of water-soluble drugs during the initial phase of their release (Yang et al., 2013). These combinations tend to flatten the shape of the release profile and produces a zero order release (Sirisolla and Ramanamurthy, 2015; Varshosaz et al., 2006). In 1997, Timmins and co-workers optimized the ratio of anionic and non-ionic polymers to obtain a pH-independent *in-vitro* release of the model drug verapamil hydrochloride. Another study has reported the retarding effect of anionic polymers like SCMC on the release of propranolol hydrochloride from matrix tablets (Takka et al., 2011). Other studies investigated the swelling behavior of matrix systems containing mixtures of HPMC and SCMC and a model soluble drug to find the correlation between the morphological behavior and the drug release performance (Conti et al., 2007).

The objective of this paper is to present formulations of controlled release properties based on tablet matrix systems for DSV utilizing hydrophilic polymers. The everted gut sac of the rat small intestine was used as reliable and reproducible *ex-vivo* method to determine kinetic parameters of drug release (Lipinski et al., 2001) to predict DSV absorption through intestinal mucosal cells and calculate the apparent permeability coefficient (P_{app}) of DSV formulations and compare it to the innovator.

2. MATERIALS& METHODS

2.1. Materials:

Desvenlafaxine succinate monohydrate, was obtained as a gift from Alembic pharmaceuticals limited, India; sodium carboxy methyl cellulose (CISME, Italy); maltodextrin M100 (Glucidex®, Roquette Pharma, France); microcrystalline cellulose ph101(Avicel, GMW, India); magnesium stearate (UNDESA, Spain); silicon dioxide (Aerosil200, OCI Company Ltd., South Korea); Methocel k15M (Dow Chemical Company, USA); ethanol lactose, sodium alginate (SA) and other chemicals (El-Nasr for chemical industries, Egypt). All chemicals were of analytical grades.

2.2. Methods

2.2.1. Preparation of DSV matrix systems

Fifteen formulations (Table I) were prepared using wet granulation technique. The calculated amount of DSV was ground in a mortar for 5 min, and then geometrically mixed with the chosen excipient (Maltodextrin, Avicel or lactose). Finally, the specified quantity of the main matrix polymer, Methocel k15M, was added at a ratio of either 1:1 or 1:1.25 (drug: polymer) and mixed for 10 min. For formulations containing SCMC or SA, the selected negatively charged polymer was added before the main matrix polymer and mixed well for 5 min.

Wet massing of mixtures was done with the required quantity of ethyl alcohol 95% and the wet mass was passed through a 0.5 mm sieve using wet granulator (Erweka FGS wet granulator, Germany). The produced granules were then dried at $50^{\circ}C$ till reaching moisture content less than 2% measured by infrared moisture balance (Kitt, Japan). The dried granules were finally passed through 0.5 mm sieve. Magnesium stearate and Aerosil200 were added to the prepared granules, mixed for 5 min and stored till compression. Tablets were compressed using single punch tablet press (TDP6 Single punch press, China) with shallow concave punch (10 mm diameter). Tablet weight was adjusted to 350 ± 5 mg and hardness of about 10 ± 2.0 KP using Vanguard hardness tester, USA.

2.2.2. Characterization of the prepared matrix granules

2.2.2.1. Physical characterization

The flow properties of the prepared granules were measured using flowability tester (BEP2 Copley Flowability Tester, UK) to determine the angle of repose. The bulk volume of granules was obtained by pouring an amount of 1 g the granules in 10 ml graduated cylinder. Volume was recorded and the bulk density was calculated. Tapped density was measured using tapped density tester (JV1000 Copley Tapped Density Tester, UK). Carr's Compressibility Index, an indication of the compressibility of a powder, was determined according to the following equation:

Carr's Index (%) =100 x (Tapped Density-Bulk density)/ Tapped density   **Equation (1)**

Where the tapped density is the increased bulk density resulting from mechanically tapping the container containing the powder sample.

2.2.2.2. Differential scanning calorimetry (DSC)

The use of negatively charged polymers (SCMC or SA) can lead to interactions with the tested cationic drug (DSV). In order to investigate such interactions, thermograms of DSV, SCMC, SA and their physical mixtures were recorded using differential scanning calorimeter (DSC 6, Perkin Elmer, USA) to test the physical state of DSV inside the matrix of prepared tablets.

DSV-polymer mixtures were prepared either by wet granulation or co-precipitation method in the same ratio utilized in the prepared formulations. In co-precipitation method, DSV was dissolved in 100 ml water with the negatively charged polymer, poured into small glass dish and left to dry at $50^{\circ}C$. The produced solid mixture was scrapped and thermally analyzed. Samples were weighed and placed into aluminum pans, which were then sealed, held at $35^{\circ}C$ for 1 min under a flow of nitrogen, and then heated to $350^{\circ}C$ at a rate of $10^{\circ}C$ /min.

2.2.2.3. Fourier Transform Infrared Spectroscopy (FTIR)

IR spectra were recorded using FT-IR spectrometer (IRAffinity-1S, Shimadzu FT-IR spectrophotometer, Japan) for DSV, SCMC, SA and their physical mixtures. Samples were finely ground with KBr (infra-red grade), and pressed into pellets and the IR spectra were taken in transmission over the range of 4000-500 cm^{-1}.

2.2.3. Characterization of the compressed matrix tablets

2.2.3.1. Drug content

Ten tablets were finely powdered and a sample of 350 mg (equivalent to 76 mg of DSV) was accurately weighed and transferred to 500 ml volumetric flask containing 250 ml of 0.9% w/v sodium chloride. The content was stirred with intermittent sonication (Branson 3510 Ultra sonic, Mexico) for 1 h to ensure complete extraction of DSV. The volume was completed with 0.9% w/v sodium chloride, filtered through 0.45μm millipore filter and DSV content was analyzed spectrophotometrically (Shimadzu UV 1800 spectrophotometer, Japan) at the predetermined λ_{max} of 231 nm of the first derivative spectrum. At this wavelength none of the excipients interfered with the calibration curve. A good linearity was obtained from 0.844 to 8.44 mg % DSV concentration with a determination coefficient (R^2) of 0.99983. The amount of DSV dissolved in the medium was determined by the following equation:

Content of DSV = (A $_{test}$ / A $_{standard}$) $\times 100$ **Equation (2)**

Where A, is the absorbance of the dissolved DSV for both test and standard.

2.2.3.2. Tablet hardness and friability

The vertically mounted tablet was squeezed using Vanguard hardness tester and the breaking load was determined in (KP).

Friability testing according to USP-XXXII, a sample of tablets corresponding to 6.5 g was taken. The tablets were carefully de-dusted prior and after testing. Tablet sample was accurately weighed and placed in the drum of Vanguard friability tester, USA. The drum was rotated100 times, tablets were accurately weighed and the percent friability was calculated by the following equation:

%Friability = [(w$_1$-w$_2$)/w$_1$] $\times 100$ **Equation (3)**

2.2.3.3. In-vitro tablet Dissolution and kinetic analysis of release data

Tablet dissolution requirements adopted by FDA (FDA, 2015) were applied to the prepared formulations. Dissolution study for the prepared formulations and the innovator containing 76 mg DSV was carried out using USP-XXXII dissolution apparatus I (Hanson research SR8 plus dissolution testing apparatus, USA) in 900 ml 0.9% w/w sodium chloride solution maintained at 37±0.5 ºC at basket speed of 100 rpm. At the designated time intervals, 10 ml of the release medium was withdrawn and replaced with the same volume of pre-heated release medium. All samples were run in triplicates, filtered through 0.45 μm membrane filters and the amount of DSV released was analyzed by measuring absorbance of the first derivative UV spectrum at predetermined λ_{max}.

Similarity factor (SF) was utilized to describe dissolution rate for each formulation compared with the innovator. This factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in percent dissolution between the two curves. It was calculated using the following equation (Shah et al., 1998):

$$SF = 50 \times \log \left\{ [1 + (1/n) \sum_{t=1}^{n} (Rt - Tt)^2]^{-0.5} \times 100 \right\}$$ **Equation (4)**

Where "n" is the number of time points, "Rt" is the percentage release value of the reference batch at time t and "Tt" is the percentage release value of the test batch at time t.

For evaluation of release kinetics, the obtained release data for formulations that passed similarity factor testing were fitted into first order, zero order and Higuchi equations. Selection of the best model was based on the comparisons of the relevant coefficients of determination. The release data were subjected to kinetic analysis using Korsmeyer–Peppas model correlating drug release to time by simple exponential equation for the fraction of drug release < 0.6.

$$F = Mt / M\infty = k \, t^n$$ **Equation (5)**

Where "Mt /M∞" is the proportion of drug released at time t, "k" is the kinetic constant and the release exponent "n" has been proposed as indicative of the drug release mechanism.

2.2.3.4. Swelling behavior and surface wetting of the matrix tablets

The formulation showing maximum similarity with the innovator, F10, was selected along with those containing the same drug/polymer ratio and negatively charged polymer to perform swelling test in 0.9% w/v sodium chloride solution. The weighed tablets were immersed in 900 ml of the medium for 10 h and at selected time intervals the swollen tablets were collected on filter paper, the wet tablet weight was determined using analytical balance. The percentage swelling of tablets was calculated from the equation:

$$\text{Percentage Swelling} = [(Wt - W0)/ W0] \times 100$$ **Equation (6)**

Where "Wt" denotes the weight of swollen tablet at time "t" and "W0" is the initial weight of tablets. Each experiment was repeated three times and the average value was taken.

A morphological study on swelling and erosion of the selected formulations was conducted using digital camera. Photographs of tablets freshly removed from the dissolution medium in an hourly basis, were taken with the same magnification and distance from the camera.

An indication of the degree of water penetration to the tabletcore was estimated by dropping one drop of 1% w/v brilliant blue in water on the tablet surface using an insulin syringe. Diameter of the colored spot on the tablet surface after 1 min gives indication about degree of surface wetting of the tablets, and hence water penetration.

2.3. Ex-vivo study using everted sacs

2.3.1. Development of HPLC method for determination of DSV

The method is based on separation of DSV using C8 column (4.6 x150 mm) 5µm. A mixture of phosphate buffer (5 mM, pH 3.8): acetonitrile (50%:50%) was used as mobile phase. The mobile phase was filtered through 0.45 µm Millipore filter and degassed before being pumped at flow rate 0.6 ml/min. The injection volume was 20 µL and the peaks were detected at 229 nm by UV detector with a total run time of 6 min. A calibration curve (peak area versus drug concentration) was constructed by running the working standard solutions of DSV for every series of chromatographed samples.

Stock standard solution was prepared by dissolving DSV in the mobile phase to a final concentration of 35.2 µg/ml. Linearity was confirmed by preparing serial dilutions of DSV over the range 4.4- 17.6 µg/ml. The method was validated according to USP-XXXII validation elements and the ICH guidelines. Specificity, accuracy and ruggedness of the method were also confirmed.

2.3.2. Preparation of everted sacs

Adult female Wistar rats weighing 150-160 g were used. All experiments were performed in strict accordance with Institutional Animal Care and Use Guidelines. After an overnight fast, rats were humanely sacrificed under thiopental anesthesia (Helmy and El-Gowelli, 2012; Samy et al., 2012) and the small intestine was quickly excised and flushed with sodium chloride solution (0.9% w/v) at room temperature. The removed intestines were immediately placed in warm (37^{0}C), freshly prepared oxygenated Ringer Locke solution. The jejunum was cut into 8-10 cm segments and gently everted over a glass rod (2.5 mm diameter). One end of each segment was closed using surgical silk thread (non-absorbable suture, 3-0, 0.2 mm diameter), filled with fresh oxygenated Ringer-Locke solution and sealed with a second silk thread. For each experiment, 16 sacs were prepared. Segments from different rats were randomly assigned to different dissolution cups to minimize biological variation (Alam et al., 2012).

2.3.3. Ex-vivo dissolution study

An *ex-vivo* dissolution study for the prepared formulation F10 matrix tablet and the innovator, each containing 76 mg DSV, was carried out using USP-XXVIII dissolution apparatus II using the pH-change method. The first step was done by placing the tested formulation in 750 ml simulated gastric fluid without enzymes (pH 1.2) maintained at 37±0.5 °C at paddle speed 60 rpm for 2 h. At designated time intervals, a volume of 10 ml of the release medium was withdrawn and replaced with the same volume of preheated release medium. All samples were filtered through 0.45 µm membrane filter and the amount of DSV released was analyzed by HPLC. The second step started after 2 h of gastric conditions and lasted for 4 h in Ringer Locke solution (USP-XXXII), pH (7.2-7.4) with a source of oxygen bubbles in the medium.

Three everted intestinal sacs each filled with 1 ml Ringer Locke solution and firmly tied from both ends by a silk thread were hanged to the paddle of the dissolution apparatus in each dissolution jar. At 1 h intervals, 10 ml of the release medium was withdrawn and replaced with the same volume of pre-warmed Ringer Locke solution. Every hour, the everted sacs taken from one cup were individually emptied into clean test tube and the volume was measured. DSV either transferred into the serosal fluid or entrapped inside the mucosal cells of the everted sac was determined using HPLC.

2.3.4. Sample preparation of DSV transferred to serosal fluid

The intestinal sacs at specified time intervals were emptied and an equal volume of acetonitrile was added to the obtained serosal fluid and the sample was centrifuged at 4000 rpm for 30 min to ensure complete precipitation of proteins and cell debris. A volume of 1 ml from the supernatant was diluted to 10 ml with purified water in volumetric flask. The amount of DSV transferred to serosal fluid was measured using the developed HPLC method and expressed as mean concentration of DSV in each sac ± SD.

2.3.5. Sample preparation of DSV entrapped in the mucosal cells

The emptied sacs were washed with 0.9% w/v saline and kept at -4 ^{0} C till measurement. Mucosal cells of the intestinal sacs were scrapped using glass slide, weighed and a specified volume of 0.9% w/v saline was added to prepare 40% homogenate. The prepared homogenate was subjected to cycles of freezing and thawing at room temperature with vortexing in order to facilitate mucosal cell rupture and release the entrapped DSV. The volume of the homogenate was accurately measured and an equal volume of acetonitrile was added and the mean DSV concentration in each sac ±SD was determined as previously mentioned.

2.3.6.1. Determination of the relative DSV amount transferred:

The comparison of DSV transferred to serosal compartment relative to donor compartment for prepared formulations was done using the following equation:

Relative DSV transferred (%) =

DSV (μg/ml) in the receiving compartment (serosal fluid) × 100

DSV (μg/ml) in the donor compartment (bulk fluid) **Equation (7)**

2.3.6.2. Comparison of the apparent permeability of the tested matrix:

The apparent permeability (P_{app}) was calculated according to the equation (Le Ferrec et al., 2001):

P_{app} = dQ/dt × 1/A(C0) **Equation (8)**

Where "dQ/dT" is the cumulative amount of drug (Q) appearing in the serosal compartment as a function of time obtained from the slope of the linear portion of the amount transported-versus-time plot, and "A" is the calculated surface area of the intestinal sac (cm^2). "C0" is the initial concentration of drug in the donor compartment (μg/ml). Since the concentration in the donor compartment was variable due to presence of sustained release dosage form, P_{app} was calculated for each interval separately.

2.3.7. Statistics

Values were expressed as mean ± SD. The data were statistically analyzed by one-way analysis of variance (ANOVA) followed by Newman–Keuls multiple comparison test with an equal sample size. The difference was considered significant when P values < 0.05 using Graph pad prism, version 3.02.

3. RESULTS AND DISCUSSION

3.1. Characterization of matrix granules

3.1.1. Physical characterization

The prepared matrix formulations were characterized for different physicochemical properties (Table II). The angle of repose of the prepared formulations varied from 22–28 ° showing excellent flow. For the same excipient, increasing DSV: Methocel ratio from 1:1 to 1:1.25 had no remarkable effect on the physical properties of the prepared formulations (Carr's index, Hausner ratio or angle of repose). Addition of the negatively charged polymers SCMC or SA in formulations F7 to F15 slightly improved the flow properties of the prepared granules as denoted in Carr's index and Hausner ratio values.

3.1.2. Estimation of possible drug-polymer interactions:

DSC studies of powdered DSV indicated a shallow melting endothermic peak at 113.3 °C and another broad peak at 236.7 °C (Fig. 1). For DSV-SCMC granulated mixture; the first endothermic peak was shifted to127.8 °C, while the other peak was formed in the range 242.9 °C. DSV-SCMC co-precipitate showed absence of the first endothermic peak of the drug and a sharp endothermic peak is formed at about 223.4 °C. This may indicate possible interaction between DSV and SCMC, which occurred during tablet exposure to the aqueous medium (Fig.1D).

For DSV-SA granulated mixture, the first endothermic peak was shifted to 105.9 °C, while the other peak was formed as a broad peak in the range 200-250 °C. For DSV-SA co-precipitate, there was no shift in the endothermic peak at 113.2 °C, but only a change in the peak area. It was also shown that the endothermic peak of DSV at 236.7 °C became very minute or almost disappeared (Fig. 2).

3.2.3. Infrared spectroscopy

FT-IR spectra of SCMC, DSV, DSV-SCMC granulated and co-precipitated mixtures are shown in Figure 3. DSV shows characteristic absorption bands at 3166.77 cm^{-1}corresponding to O-H groups. Another characteristic band at 1654.33 cm^{-1} which characterize C=O group of carboxylate anion found in the succinate salt (Fig. 3A). Alternatively, SCMC typically shows characteristic absorption bands at (3100-3550) cm^{-1}relative to O-H groups. Other absorption bands at 1155.34, 1269.89, 1325.99 and 1420.99 cm^{-1}were attributable to the (C–O-C) groups. Another characteristic band at (1604-1690) cm^{-1} attributable to C=O group (Fig. 3B). DSV-SCMC granulated mixture almost shows no change in the absorption bands of DSV and SCMC mentioned above (Fig. 3C), whereas, the DSV-SCMC co-precipitate shows complete masking of the absorption bands, which characterizes DSV and SCMC (Fig. 3D).

In case of SA, typical characteristic absorption bands were seen at (3094-3415) cm^{-1} relative to the OH groups. Absorption bands at 1176.1 cm^{-1} and 1426.38 cm^{-1} attributable to (C–O-C) groups. Another characteristic band was attributed to C=O group at 1645.01 cm^{-1} (Fig. 4B).

DSV-SA granulated mixture shows slight shift of O-H group to 3182.43 cm^{-1}, while the characteristic band of C=O group appears at 1647.8 cm^{-1}.DSV-SA co-precipitate shows a shift of C=O group to 1625.49 cm^{-1} together with band broadening of O-H group that appeared at 3436.94 cm^{-1} indicating a possible drug polymer interaction.

3.2. Characterization of prepared Tablets

The prepared formulations were successfully transformed into tablets. This good compressibility of the prepared formulations may be attributed to the presence of inter-particular voids as evidenced by the calculated Carr's index.

3.2.1. Drug content

All prepared formulations showed good homogeneity of DSV within the compressed tablets, where the drug content of the prepared formulations was within the range of100±5%.

3.2.2. Hardness and friability of the compressed tablets

Hardness of the compressed tablets was adjusted at the range of 10±2 Kp. This was assured by measuring tablet hardness for each compressed formulation. Friability of the compressed tablets was less than 1%.

3.2.3. In-vitro drug release

According to the FDA (2015), 0.9%w/v sodium chloride was considered the most suitable dissolution medium for DSV. Figure 5a shows the percentage cumulative DSV release of formulations F1-F3compared to the innovator. It was clear that the innovator release was slower than the formulations containing DVS: Methocel ratio of 1:1. To obtain a slower release, the ratio of Methocel was increased to be 1:1.25 (F4-F6). The higher concentrations of Methocel resulted in slower release (Fig.5b) that was still slightly higher than the innovator. Alternatively, formulations containing lactose (F4 and F6) showed the highest release, which can be attributed to the water solubility of lactose. The slowest release of DSV was from matrices containing maltodextrin (F1, F4) possibly due to the small aqueous pores found in case of maltodextrin due to gel formation upon contact with water, which can form coherent diffusion barrier that delays further percolation of the hydration medium (Chronakis, 1998; Levina and Rajabi-Siahboomi, 2004; Mason et al., 2015). It has been reported that modified starches (maltodextrins) could be used efficiently in the reduction of drug release rate from controlled release tablets because of their cold water-swelling capacity forming gel barrier (Bravo et al., 2002; Nickerson et al., 2006).

Another trial to modulate DSV release was made by incorporating the negatively charged polymer SCMC while keeping the 1:1 drug: polymer ratio (F7-F9). It was shown from figure 5c that F7 release was close to that of the innovator, while F8 and F9 (containing Avicel or lactose, respectively) were faster than the innovator.

Upon combining the effect of the high polymer ratio (Drug: Methocel ratio of 1:1.25) and the addition of negatively charged polymers SCMC (F10-F12) or SA (F13-F15) the release pattern of DSV could be greatly modulated with the disappearance of the initial burst of DSV in the first hour of release (Fig.5d-e). The slowest release profile was obtained when both Methocel and SCMC or SA were used in the formulation, where 100% of the drug

dissolution occurred after 24 h. This indicated potential synergistic interaction (chemical and/or physical) between drug–polymer and/or polymer–polymer. This was supported by the obtained thermograms of DSV, SCMC, SA, and mixtures of DSV with these negatively charged polymers. Notably, in other studies where SCMC formulations with hydrophilic polymers (HPMC) and propranolol HCl were investigated, it was suggested that dissolution was mainly controlled by an interaction between the cationic drug and the anionic polymer (Nickerson et al., 2001).

According to the semi-mechanistic model conducted by Franek et al., 2015, our results of a more delayed drug release are more preferable compared to faster release preparations. This is mainly due to the suggestion that desvenlafaxine absorption from Immediate Release Formulation (IRF) is rate-limited by permeability, whereas desvenlafaxine absorption from Extended Release Formulations (ERF) is likely rate-limited by dissolution due to the formulation. Consequently, the prepared formulations can provide a better modulation of drug release that may eliminate any release-related side effects by simple changes in the used matrix.

3.2.4. Estimation of similarity factor values comparing with innovator product

The value of Similarity Factor (SF) is a good parameter for comparison of release data as it takes into consideration all release points rather than a single one. The results of dissolution studies were expressed in terms of similarity factor values comparing with innovator results at different time intervals. Similarity factor values greater than (50) ensure equivalence of the two curves (Shah et al., 1998), the tested formula and the innovator product.

For the same type of matrix excipient, formulations containing higher concentration of Methocel had greater similarity factor than those containing lower concentration. Generally, for the same drug: polymer ratio, the tested matrix excipients can be ranked according to their similarity of DSV release pattern compared with the innovator as follows: maltodextrin (F1, F4, F7 and F10) > Avicel (F2, F5, F8 and F11) > lactose (F3, F6, F9 and F12). This rank is supported by the calculated values of similarity factor.

Of the tested formulations only four formulations had SF higher than 50, namely F7, F8, F10 and F11 with SF of 76.4, 53.6, 84.7 and 66.6, respectively. Another ranking of similarity can be done to compare the effect of incorporation of negatively charged polymers (Table III). Of all the tested formulations, F10 showed the highest similarity factor (SF= 84.68) at DVS: Methocel ratio of 1:1.25, which was selected to be of optimum compositions.

3.2.5. Calculation of release kinetics

In order to investigate the mode of release of DSV from the prepared controlled-release formulations, the release data were analyzed with various mathematical models. The (r^2) of various models was calculated for the formulations containing maltodextrin and high SF with the innovator (F7, F10, F14 and F15). They were ranked in order of: Korsmeyer> Higuchi > first order > zero order >Hixson-Crowell.

Since the release exponent was found to be $0.45 < n < 0.89$, thus release of DSV is done mainly by Korsmeyer Peppas mechanism from these formulations. This means that the drug transport mechanism is an anomalous transport drug release by a non-Fickian diffusion in which both drug diffusion and polymer erosion contribute to drug release.

3.2.6. Swelling behavior of the compressed tablets

A comparative swelling study (Fig.6) was performed for the innovator against F10, F11 and F12 containing different matrix excipients (maltodextrin, Avicel and lactose, respectively), high polymer content (drug: polymer ratio of 1:1.25) and one negatively charged polymer (SCMC). The F10 formula containing maltodextrin as a matrix excipient showed swelling behavior that was very close to that of the innovator product followed by F11 containing Avicel. The percentage swelling in case of F10 and F11 was higher than that of the innovator, where it increased gradually by time but in a faster rate in case of F11. Conversely, addition of lactose as matrix excipient in F12 showed a very rapid swelling, which reached a maximum after 4 h followed by gradual decrease possibly due to the high water solubility of lactose.

When hydrophilic matrix tablets are placed in 0.9% w/v sodium chloride solution, the solution starts to penetrate the matrix creating a dynamic process involving: polymer wetting, polymer hydration, gel formation, swelling and polymer dissolution. The polymer quickly hydrates on the outer tablet skin to form gelatinous layer. A rapid formation of this gelatinous layer is critical to prevent wetting of the interior and disintegration of the tablet core. Once the original protective gel layer was formed, it controls the penetration of additional water into the tablet (Mason et al., 2015).

During the process of polymer hydration, soluble excipients or drugs are also wetted, dissolved and start diffusion out of the matrix, while insoluble materials are held in place until the surrounding polymer/excipient/drug complex is eroded or dissolved away. This is why the mechanisms by which drug release from matrix tablets are dependent on the rate and extent of each of these stages.

Modified starch (maltodextrin) is characterized by rapid formation of the outer gelatinous layer due to its swelling behavior, which prevents rapid penetration of dissolution medium inside the tablet core barrier (Bravo et al., 2002; Nickerson et al., 2006). This can explain the slow swelling of the other matrix excipients utilized in formulations F11 and F12.

The three tablet formulations F10, F11 and F12 were examined just after being removed from the soaking medium on an hourly basis. Lactose, a water-soluble excipient with hydrophilic nature, creates high osmotic pressure inside the swelled matrix forming more micro-cavities in polymer matrices, facilitating gel formation and shortening the penetration time of the dissolution medium into the matrix. Moreover, this soluble substance acts as a channeling agent by rapidly dissolving and easily diffusing outward, therefore decreasing tortuosity and/or increasing the matrix porosity (Sangalli et al., 2001). This explains the higher swelling and erosion of matrix polymer in case of utilizing lactose as matrix excipients than Avicel and maltodextrin.

The ability of tablets to absorb water is another factor that can affect drug release. This was examined by visual estimation of the diameter of a colored spot formed on tablet surface after one minute upon adding one drop of brilliant blue solution on the tablet surface using an insulin syringe. Tablets containing maltodextrin as matrix excipient showed the slowest penetration rate followed by Avicel then lactose; this was observed from the diameter of the formed colored spot (Fig. 7).

3.3. Ex-vivo dissolution study

The amount of DSV released in simulated gastric fluid (pH 1.2) in the donor compartment from F10 (matrix tablet) was almost the same as the innovator (Table IV). DSV released after pH change to 7.4 was also determined in the bulk solution outside the sacs for the two formulations.

DSV release from the matrix tablet and the innovator product in case of pH gradient method was the same as that obtained by the method adopted by FDA using 0.9% w/v sodium chloride as dissolution medium. Thus, it can be concluded that the release of DSV from the matrix tablets either the innovator or F10 was pH-independent. After 6 h about 54 μg/ml of DSV was released from either F10 or innovator. Since the concentration in the donor compartment was variable with continuous drug release from the dosage form, dQ/dT (the change in serosal concentration) was calculated from the slope for each interval separately.

Within an *in-vitro* system, P_{app} is useful parameter to compare the permeability of different drug molecules (Le Ferrec et al., 2001). The average P_{app} of DSV released from the prepared formula was 1.234×10^{-5} cm/s. This is closely approaching the value of P_{app} for mannitol (1.7×10^{-5} cm/s) that represents a good permeability marker for hydrophilic compounds (Brown et al., 2002; Vora et al., 2015). Similarity factor of P_{app} of the prepared formulation calculated at different time intervals was very high (99.9987) indicating a close similarity between apparent permeability of DSV released from the tested formulation to that of the innovator.

After 4 h the amount transferred relative to the donor compartment exceeded 80% for the tested formulation F10 (Fig. 8) and there was no significant difference between the prepared formulation and the innovator at the end of simulated intestinal fluid period. This indicated good absorption of DSV from the prepared formulations in to the intestinal sacs.

4. CONCLUSION

The formulation of DSV in a hybrid matrix using the hydrophilic polymer Methocel, maltodextrin excipient and the negatively charged polymer SCMC seems to be a successful and simple technique to modulate drug release and prevent the initial burst. The prepared granules were successfully compressed into tablets having a pH-independent release and excellent intestinal absorption. The obtained results could be used as a platform for modulating the release of similar hydrophilic drugs whose side effects are related to the release pattern.

5. Conflict of Interest statement

None

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Legend to Figures

Figure 1: Thermal analysis of (A) DSV, (B) CMC, (C) DSV-CMC granulated mixture, (D) DSV-CMC co-precipitate.

Figure 2: Thermal analysis of (A) DSV, (B) SA, (C) DSV-SA granulated mixture (D) DSV-SA co-precipitate**.**

Figure 3: Infra-red charts of (A) DSV, (B) SCMC, (C) DSV-CMC granulated mixture and (D) DSV-CMC co-precipitate.

Figure 4: Infra-red charts of (A) DSV, (B) SA, (C) DSV-SA granulated mixture and (D) DSV-SA co-precipitate.

Figure 5: *In-vitro* DSV release pattern from different matrix tablets

Figure 6: Percentage swelling of different DSV matrix tablet formulations (F10, F11 and F12) compared with the innovator in 0.9% w/v sodium chloride at 37 ^{0}C (Table 1).

Figure 7: Surface wetting and penetration of brilliant blue solution to the prepared matrix tablets containing different matrix excipients.

Figure 8: Percentage cumulative DSV absorbed from mucosa and passed to the serosal compartment relative to donor compartment of F10 and the innovator.

Figure 1

(A) DSV

Onset = 99.663 ^{0}C
End = 128.367 ^{0}C
Area = 446.632 mJ
Delta H = 89.326 J/g
Peak = 113.266 ^{0}C
Peak Height = 4.1994 mW

Onset = 187.773 ^{0}C
End = 293.452 ^{0}C
Area = 1566.080 mJ
Delta H = 313.216 J/g
Peak = 236.700 ^{0}C
Peak Height = 4.3644 mW

Peak = 302.278 ^{0}C
Peak Height = -2.327 mW

Onset = 278.463 ^{0}C
End = 321.031 ^{0}C
Area = -274.046 mJ
Delta H = -74.809 J/g

(B) CMC

(C) DSV-CMC (granulated mixture)

Onset = 115.508 ^{0}C
End = 131.611 ^{0}C

Area = 924.519 mJ
Delta H = 184.904 J/g
Peak = 127.775 ^{0}C
Peak Height = 6.8761 mW

Onset = 221.879 ^{0}C
End = 276.378 ^{0}C

Area = 1735.865 mJ
Delta H = 347.173 J/g
Peak = 242.919 ^{0}C
Peak Height = 6.9940 mW

(D) DSV-CMC (Co-PPT)

Onset = 221.147 ^{0}C
End = 225.318 ^{0}C
Area = 19.469 mJ

Delta H = 3.894 J/g
Peak = 223.423 ^{0}C
Peak Height = 1.1249 mW

Figure 2

Onset = 99.663 °C
End = 128.367 °C
Area = 446.632 mJ
Delta H = 89.326 J/g
Peak = 113.266 °C
Peak Height = 4.1994 mW

Onset = 187.773 °C
End = 293.452 °C
Area = 1566.080 mJ
Delta H = 313.216 J/g
Peak = 236.700 °C
Peak Height = 4.3644 mW

Peak = 302.278 °C
Peak Height = -2.327 mW

Onset = 278.463 °C
End = 321.031 °C
Area = -274.046 mJ
Delta H = -74.809 J/g

(A) DSV

Onset = 56.593 °C
End = 136.961 °C
Area = 184.184 mJ

Delta H = 368.237 J/g
Peak = 100.968 °C
Peak Height = 6.0370 mW

(B) SA

Onset = 98.420 °C
End = 112.556 °C
Area = 128.698 mJ
Delta H = 25.740 J/g

Peak = 105.948 °C
Peak Height = 2.606 mW

(C) DSV-SA (granulated mixture)

End = 124.424 °C

Onset = 96.410 °C

Area = 435.778 mJ
Delta H = 87.166 J/g

Onset = 55.076 °C
Area = 808.156 mJ
Delta H = 161.631 J/g

Peak = 113.332 °C
Peak Height = 4.2615 mW

(D) DSV-SA (Co-PPT)

Figure 3

(A) DSV

(B) CMC

(C) DSV-CMC (granulated mixture)

(D) DSV-CMC (Co-PPT)

Figure 4

(A) DSV

(B) SA

(C) DSV-SA (Granulated mix)

(D) DSV-SA (Co-PPT)

Figure 5

Figure 6

Figure 7

Figure 8

Table I: Composition of different DSV matrix systems*.

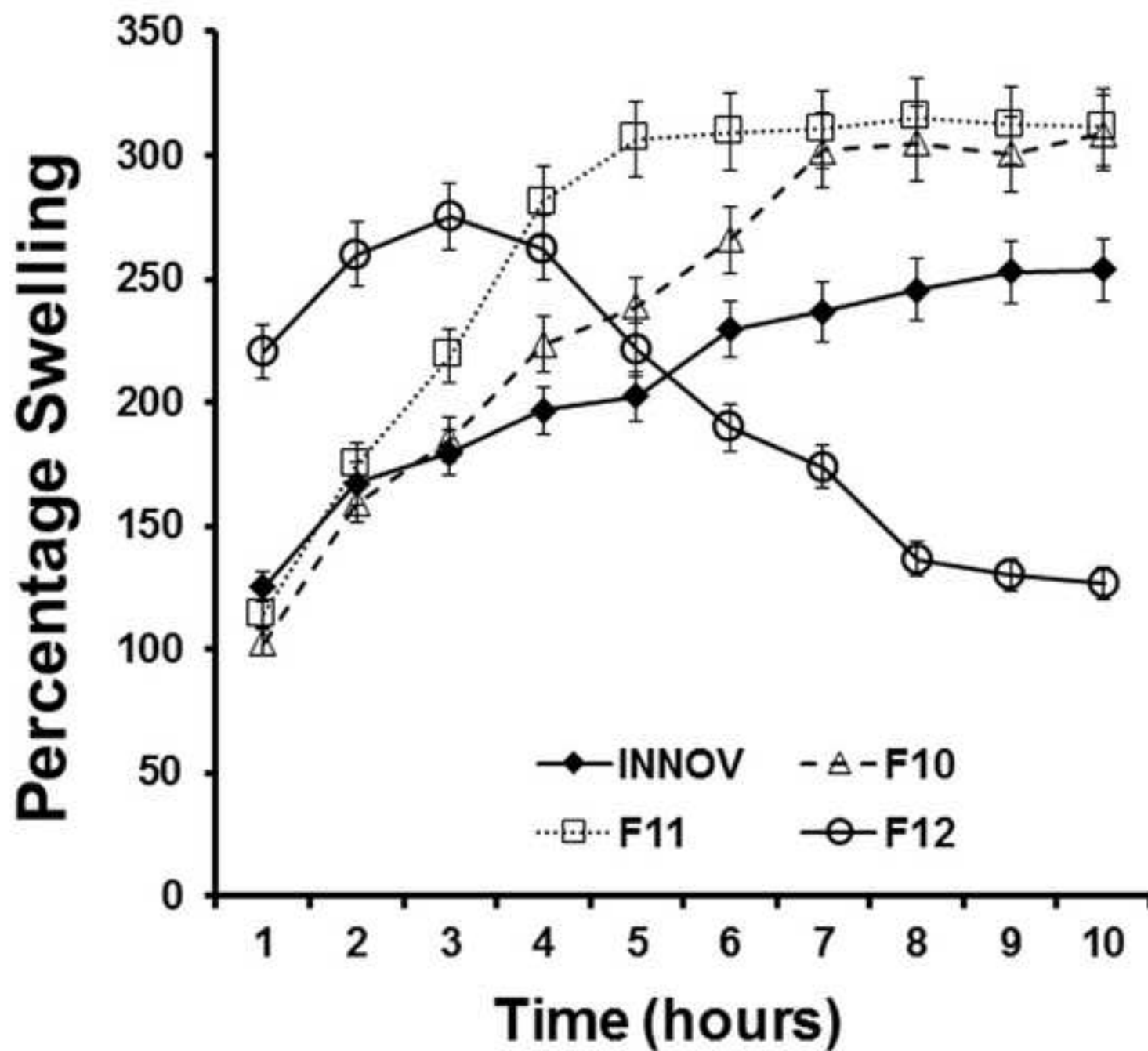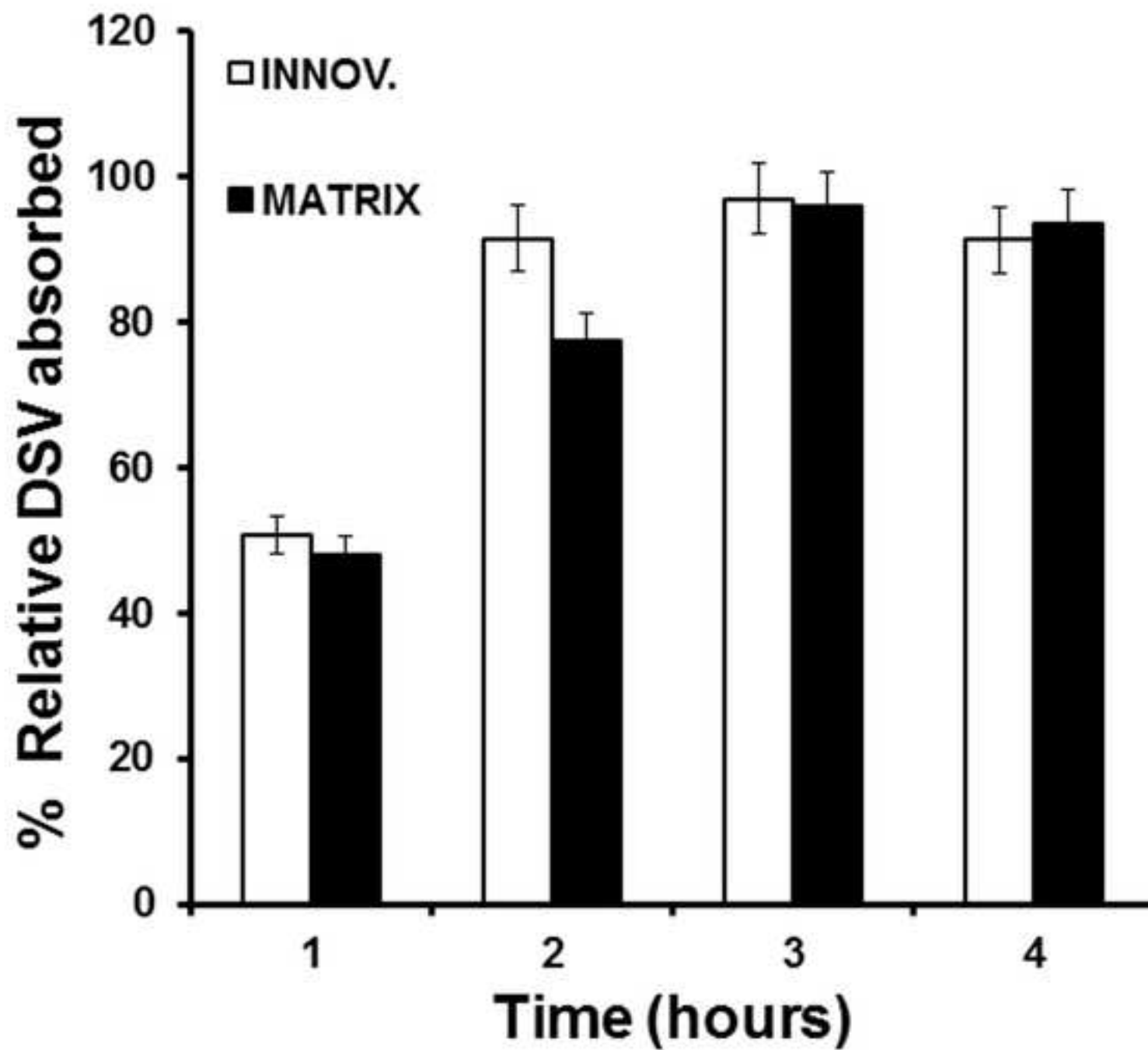| Formula code	Methocel k15 M	SCMC	SA	Maltodextrin M100	Avicel ph101	Lactose monohydrate
F1	76	---	---	193	---	---
F2	76	---	---	---	193	---
F3	76	---	---	---	---	193
F4	95	---	---	174	---	---
F5	95	---	---	---	174	---
F6	95	---	---	---	---	174
F7	76	76	---	117	---	---
F8	76	76	---	---	117	---
F9	76	76	---	---	---	117
F10	95	76	---	98	---	---
F11	95	76	---	---	98	---
F12	95	76	---	---	---	98
F13	95	---	7.6	166.4	---	---
F14	95	---	15.2	158.8	---	---
F15	95	---	22.8	151.2	---	---

*An amount of 76 mg DSV were incorporated in each formula. A quantity of 1.5 mg Aerosol200 and 3.5 magnesium stearate were added to each formulation to obtain a final tablet weight of 350 mg.

Table II: Physical properties of the prepared matrix granule formulations

Formula code	ρ_o (g.ml^{-1})	ρ_t (g.ml^{-1})	Hausner's ratio	Carr's Index		Angle of repose (ө)
F1	0.32±0.12	0.42±0.12	1.31	23.51	(pass)	25.64±0.20 (Excellent)
F2	0.32±0.10	0.41±0.10	1.27	21.37	(pass)	28.44±0.18 (Excellent)
F3	0.40±0.15	0.51±0.15	1.27	21.21	(pass)	22.93±0.23 (Excellent)
F4	0.39±0.14	0.52±0.14	1.32	24.32	(pass)	22.62±0.17 (Excellent)
F5	0.39±0.15	0.53±0.15	1.33	24.71	(pass)	23.75±0.22 (Excellent)
F6	0.39±0.11	0.51±0.11	1.27	21.30	(pass)	25.56±0.17 (Excellent)
F7	0.42±0.12	0.51±0.12	1.21	17.54	(Fair)	22.90±0.19 (Excellent)
F8	0.41± 0.12	0.50 ±0.12	1.22	17.80	(Fair)	26.56±0.19 (Excellent)
F9	0.42± 0.08	0.50±0.08	1.22	18.20	(Fair)	24.62 ±0.21 (Excellent)
F10	0.41±0.08	0.49 ±0.08	1.20	16.46	(Fair)	25.64 ±0.22 (Excellent)
F11	0.39 ±0.11	0.47 ±0.11	1.19	16.00	(Fair)	22.61 ±0.21(Excellent)
F12	0.44 ±0.12	0.53 ±0.12	1.22	18.11	(Fair)	26.56 ±0.17 (Excellent)
F13	0.39 ±0.12	0.49 ±0.12	1.25	20.40	(Fair)	27.55 ±0.18 (Excellent)
F14	0.37± 0.13	0.47± 0.13	1.25	20.12	(Fair)	24.44 ± 0.18 (Excellent)
F15	0.36± 0.09	0.45± 0.09	1.25	20.00	(Fair)	23.49 ± 0.20 (Excellent)

ρ_o: bulk (pour) density* ρ_t: tapped density**

Table III: Effect of negatively charged polymers and matrix excipients on similarity factor of DSV dissolution profiles from different formulations compared with the innovator.

DSV:Methocel ratio	Matrix excipient	Formulation rank	Corresponding similarity factor	Negatively charged polymer utilized
1:1	Maltodextrin	F7 > F1	76.357 > 46.518	SCMC
1:1	Avicelph 101	F8 > F2	53.620 > 42.387	SCMC
1:1	Lactose	F9 > F3	39.256 > 33.725	SCMC
1:1.25	Maltodextrin	F10 > F4	84.680 > 48.539	SCMC
1:1.25	Avicelph 101	F11 > F5	66.538 > 42.261	SCMC
1:1.25	Lactose	F12 > F6	40.671 > 37.646	SCMC
1:1.25	Maltodextrin	F14 > F4	60,140 > 48.539	SA
1:1.25	Maltodextrin	F15 > F4	53.764 > 48.539	SA

Table IV: Ex-vivo DSV permeation into different compartments and the calculated donor compartment, mucosal cells and serosal fluid concentrations at different time intervals

Time	Release medium pH	Formula	DSV concentration			dQ/dT µg/min	$P_{app} \times 10^{-5}$ cm/s
			Donor µg/mL	Mucosal cells µg/g	Serosal fluid µg/mL		
1 h	(pH1.2)	Innov.	18.76± 0.63				
		F10	20.64± 0.76				
2 h	(pH1.2)	Innov.	25.30 ± 0.53				
		F10	21.20 ±0.50				
3 h	(pH7.4)	Innov.	36.10 ± 0.30	33.26± 0.014	18.37 ±7.44	0.306	2.5
		F10	35.20 ± 0.45	119.83±0.022	16.96 ± 3.70	0.282	2.4
4 h	(pH7.4)	Innov.	44.75 ± 0.54	102.38±0.041	40.95 ±3.07	0.376	1.9
		F10	44. 0 ± 0.60	134.21±0.021	34.10 ± 6.01	0.285	1.0
5 h	(pH7.4)	Innov.	49.80 ± 0.95	132.76±0.011	48.30 ± 5.00	0.122	0.50
		F10	49.00 ± 0.90	176.83±0.011	47.01 ± 1.73	0.215	0.85
6 h	(pH7.4)	Innov.	54.80± 0.65	223.55±0.050	50.08 ±4.40	0.029	0.12
		F10	53.60± 0.62	196.75±0.196	50.19 ± 2.73	0.053	0.19