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Exploring the potential of tianeptine matrix tablets: Synthesis, physico-chemical characterization and acute toxicity studies

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Abstract: The main objective of the present study was to explore the potential of matrix tablets as extended release dosage form of tianeptine, using HMPC K100 as a polymer. HPMC K100 extended the release of the drug from formulation due to the gel-like structure. Direct compression method was adopted to compress the tablets using different concentrations of polymer. Tablets were evaluated for pre-compression and post-compression parameters. Drug release study showed that tablet extends the release of drug with the increasing concentration of polymer. Drug, polymers and tablets were analyzed and/or characterized for compatibility, degradation, thermal stability, amorphous or crystalline nature via FTIR, DSC, TGA, XRD studies. SEM study predicted that tablets had a uniform structure. HPMC K100 based tablets were similar to that of the reference product. Acute toxicity study conducted on Swiss albino mice showed that matrix tablets were safe and non-toxic, as no changes in physical activity and functions of organs were observed. Biochemical and histopathological study revealed lack of any kind of abnormality in liver and renal function. Moreover, necrotic changes were absent at organ level.

Keywords: Tianeptine sodium, extended release, tablets, compression, toxicity.

INTRODUCTION

Extended release dosage form is any dosage form that prolongs the drug's therapeutic activity. Extended release (ER) terminology is always relevant to prolongation of the duration of the drug action, having maintained drug concentration over the course of drug administration. ER has drug reproducibility and predictability, while justifying release of kinetic behavior. A successful extended release formulation development requires perfect knowledge of pKa, permeability, solubility, half-life and physiochemical properties of the drug used in the formulation. ER is sensitive to changes in GI motility, pH, GI fluid along with their composition (Nart, 2017; Fukui, 2017). It gained popularity due to high drug loading capability, which permits daily administration of drug once, while comparing the conventional dosage form where frequent administration, unpredictable peak plasma concentration (C_{max}) are considered to be major drawbacks (Nart, 2017; Pundir *et al.*, 2017; Dash and Verma, 2013).

Sometimes, ER formulation did not provide desired C_{max} due to physical and chemical interactions of the dosage form with intestinal fluid, gut motility, pH of gastric fluid, presence of food, co-administration of drugs like proton pump inhibitors, H_2-receptor antagonists and antacids, and many times due to the pathological state of the gut. Aforementioned physiochemical factors are crucial in determining the physical state of the drug and C_{max}; drug dissolution rate is altered due to these factors. Alcohol dose dumping is the main parameter in altering C_{max} due to rapid release of the drug from extended release dosage form (Klein *et al.*, 2018; Lazzari, 2018).

If a matrix system is desirable, then disperse the drug into the polymeric skeleton where the molecules are embedded into the matrices of the polymer. They may swell up or erode on contact with the dissolution media. Matrix system is obtained when the drug is dispersed in the polymer matrices, which upon contact with the dissolution media are hydrated and swell up specially, if incorporated polymer is hydrophilic in nature (Lazzari, 2018).

Matrix system is becoming popular in designing controlled release drug delivery system due to the ease of manufacturing, limited risk of dose dumping and least fluctuation in peak plasma concertation. Drugs having high and low water solubility are considered to be good candidates for the matrix system, especially in combination with water-repelling and water-loving polymers. Matrix system is of two types: i) hydrophilic ii) hydrophobic; based on the type of polymer selected for the study (Ofori-Kwakye *et al.*, 2016). A variety of

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polymers from natural and synthetic sources either alone or in combination are used for the development and/fabrication of ER system. Most widely used polymers include gums, cellulose and polyethylene oxide derivatives (Khlibsuwan, 2016). ER dosage form for the drugs belonging to a different therapeutic class has been investigated for in-vitro and in-vivo studies.

From matrix system drug release via degradation is followed by diffusion, glass rubber transition or erosion. Upon contact with the dissolution media; it penetrates into dosage form inside the core, which absorbs water and swells up (Bose *et al.*, 2013). As swelling results in increased volume, it will decrease the rate of drug release from the core to the media. The more the swelling, the more will be the glass rubber transition phenomenon in which polymers have gel-like appearance leading to decrease in drug release from the dosage form or device due to increase in diffusion path length and thickness, a rate limiting step in drug release. Erosion occurs when polymer particles dislodge from the surface in the form of tiny fragments to ensure drug release in the dissolution media upon contact. Whatever the mechanism of drug release from the matrix system (fig. 1); understanding of formulation factors, dissolution media, environmental factors and substance properties are key elements to explain it thoroughly (Timmins *et al.*, 2016).

Matrix tablets could be prepared by wet, dry granulation and direct compression method (DCM). DCM is preferred due to the ease of manufacturing and process parameters. This method is also suitable for heat and moisture sensitive drugs to enhance the dosage form stability, where it is subjected to degradation under environmental hazards. DCM is also preferable owing to the two-step method to manufacture tablets; mixing and compression. DCM is challenging if powder blend has poor flowability, low content uniformity, weight variation, low mechanical strength and dissolution properties (Komersova *et al.*, 2016; Ofori-Kwakye *et al.*, 2016).

Tianeptine sodium (TS) is an anti-depressant drug having opioid receptor activity prescribed for bipolar depression, mania, treatment resistant depression, anxiety, pain management in bowel syndrome and asthma (Bilge *et al.*, 2012; Lombard, 2018; McEwen *et al.*, 2010; Wilde and Benfield, 1995). Hydroxypropylmethyl cellulose (HPMC K100) is a water-loving polymer widely used in the matrix system to prepare the tablets by the researchers to control the release profile of drugs over the extended time period.

The current study aimed to design extended release matrix tablets of tianeptine sodium using varying blends of hydrophilic polymer. The objective was to enhance drug release modifying properties of polymer leading to formation of optimized formulation of tianeptine sodium.

METARIALS AND METHODS

Material

All ingredients used in the formulation are shown in table 1. Accurately weighed amount of drug and excipients used in the study were mixed manually in pestle mortar geometrically for 20 min. Then the powder blend was lubricated with magnesium stearate for 5 min and subjected to direct compression using the rotary die punch machine ZP-19 for tablet formation.

Particles characterization analysis

After weighing all ingredients, powder blend was evaluated for pre-compression parameters; bulk density, tapped Density, hausner Ratio, angle of repose (Abdus Salam *et al.*, 2018; Nair *et al.*, 2019). Fourier transform infrared (FTIR), DSC, TGA and X-RAY diffraction (XRD) were used for analysis of drug, polymer, physical mixture and final product.

Fourier transformed infrared spectrophotometry, Differential scanning calorimetric analysis and Thermogravimetric analysis

FTIR spectrums were taken using IR (Affinity-1, Shimadzu, Kyoto, Japan) to determine the presence of specific functional groups in the drug, polymer, physical mixture and tablet (M5). Data collection software was used to evaluate interactions among the ingredients. Small amount of powdered samples were directly placed onto pike miracle ATR cell and scanned over a range of 4000 cm^{-1} to 600 cm^{-1}(Dave *et al.*, 2017; Rangu *et al.*, 2018).

DSC thermogram of studied samples was recorded using a differential scanning calorimeter (DSC-SDT Q600 V8.2 Tokyo Japan). An accurately weighed sample of 2.5 mg was placed into aluminum pan and measurements were performed over a temperature range of 0-400°C at a heating rate of 10°C min^{-1} (Dave *et al.*, 2017).

TGA (SDT Q600 V8.2) was conducted to check the thermal stability of drug, polymer, physical mixture and tablets. All samples were tested at 0-400°C along with heating rate of 20 °C/min, using nitrogen gas as inert gas; favoring sublimation at high temperature of many organic compounds when it is carbonized (Huang *et al.*, 2018).

X-RAY diffraction (XRD)

XRD (PANalytical Empyrean, Almelo, Netherlands) was carried out to determine the crystalline structure of the drug, polymers and formulation. Samples were run at Cu-Kα radiation and graph was plotted using the Origin Pro software.

Flowability determination

Flow properties of powder blend was determined in order to estimate flow behavior. It is observed that particle size and shape both affect flow behavior of the powdered

material. Angle of repose was calculated through funnel method. Powder was freely passed through the funnel under gravitational force to form the heap on a smooth and horizontal surface. Diameter and height of formed heap was calculated (Maheshwari *et al.*, 2018).

Angle of repose= $\tan^{-1}(height/diameter)$ [1]

Bulk and tapped densities were measured using volumetric cylinder of 20mL. Calculated amount of powder was placed in the cylinder and initial volume was noted. Cylinder was tapped on a smooth surface till the powder volume inside the cylinder became constant. Bulk and tapped density were calculated for every formulation. (Maheshwari *et al.*, 2018; Pandey *et al.*, 2019). Using bulk and tapped density values; compressibility index and hausner ratio were calculated.

Bulk density = $\frac{weight\ of\ powder}{bulk\ volume\ of\ powder}$ [2]

Tapped density= $\frac{weight\ of\ powder}{tapped\ volume\ of\ powder}$

Compressibility index = $\left(\frac{bulk\ volume\ of\ powder - tapped\ volume\ of\ powder}{bulk\ volume\ of\ powder}\right)100$ [3]

Hausner ratio= $\frac{bulk\ volume\ of\ powder}{tapped\ volume\ of\ powder}$ [4]

Each parameter for the above-mentioned test was performed in triplicate.

Physical properties of directly compressed tablets

Post-compression parameters include thickness, hardness, friability, dissolution and stability studies.

Thickness and hardness

Monsanto hardness tester (PX/THT-3957 India) was used to measure thickness and hardness (Rangu *et al.*, 2018). Tablet friability was measured by Roche friabilator. Average weight of 20 tablets was taken and placed into the apparatus, rotating at 25 r.p.m. When the tablets fell downward and underwent abrasion, they were removed, dedusted and weighed again. Percentage friability was calculated using the following formula. Friability must be ≤ 1(Rangu *et al.*, 2018; Pandey *et al.*, 2019).

%age friability = $\left(\frac{initial\ weight\ of\ tablets - final\ weight\ of\ tablets}{initial\ weight\ of\ tablets}\right) * 100$ [5]

Friability defines the durability of tablets during handing and transportation.

Weight variation test

Weight variation test was done to determine the variation in weight of directly compressed tablets. To perform it, 20 tablets were taken randomly and individually weighed; then their average weight was taken using electronic analytical balance. Weight variation was calculated by following equation:

% Weight variation = $\frac{(individual\ weight\ of\ tablets - average\ weight\ of\ tablets)}{(average\ weight\ of\ tablets)} * 100$ [6]

The tablets met the USP test if not more than two were outside the percentage limit and if no tablet differed by more than two times the percentage limit. Weight variation tolerance for uncoated tablets differs according to tablet weight (Rahamathulla, 2019).

Content uniformity of directly compressed tablets

Content uniformity means uniform distribution of all particles in directly compressed matrix tablets. To perform this test, tablets were taken and crushed manually to obtain fine powder, followed by sieving. An amount of the powder mass equivalent to the weight of a single tablet was taken and dissolved in solvent to form solution. Prepared solution was filtered, sonicated for 15 min and absorbance was taken on UV spectrophotometer (Shimadzu Japan) at 254 nm (Naeem *et al.*, 2010).

Dissolution study

Drug release studies were carried out using pharma test dissolution apparatus U.S.P. type II. Initial study for two hours was performed in 0.1N HCl and rest of the study was completed in phosphate buffer (pH 7.2). At specified time intervals of 0.5, 1, 2, 3, 4, 5, 6, 7, 8 and 12 hours, 5mL of sample was withdrawn, filtered and then run on the spectrophotometer to take absorbance. An equivalent volume of buffer was used to replenish the withdrawn volume (Komersova *et al.*, 2016). Similarity factor was calculated using the following equation.

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \quad [7]$$

Where Rt and Tt are percentages of drug release from reference and test tablets at time intervals t and n is the number of sampling points (Huang *et al.*, 2018).

Toxicity studies

Toxicity studies were approved and conducted according to research ethics established by the institutional review board of the pharmacy and research ethics committee (Ref#602 GCUF/ERC/2002) of Govt. College University, Faisalabad, Punjab, Pakistan in accordance with OECD guidelines. Animals were properly handled in accordance to the agreement with UK Animals Act 1986 for scientific procedure (Botham, 2004).

Study design

Swiss albino mice (procured from the University of Agriculture, Faisalabad) were selected for acute toxicity studies of developed dosage form. Female Swiss albino mice were divided into two groups; control (C) and test (T) groups with six mice each. Average weight of mice was 174.3g ± 3.5 - 174.5g ± 3.3 and 173.7g ± 8.5 in C and T groups respectively. They were kept in wire cages under controlled atmospheric conditions i.e. 22ºC ± 3ºC and relative humidity 30% in animal house under 12 hours dark and light cycle. They were provided with

sterile food, unlimited supply of water and the bedding of cages was changed over 24 hours. They were evaluated physically for any kind of alignment, activity and feeding habit and had free access to water and food in the cage. Dose calculation was done according to OECD guidelines higher than the therapeutic dose of TS considering the body weight of each mice in each group. Calculated dose of 25 mg/kg was dissolved in distilled water using vortex mixing. C group was administered with distilled water. T group was administered with dose using gastric gavage.

Followed by dose administration, mice were monitored for changes in physical activity, gate, sensation, sedation, tremors, secretions (salivation, sweating, lacrimation) excretions, body weight, food and water consumption for 14 days. At the end of the study, blood samples were collected for hematological and biochemical analysis. Animal slaughtering was done for histopathological examination. Vital organs were preserved in formalin (10%) solution for histopathological examination (Mahmood *et al.*, 2016).

Hematological study (CBC) was performed to measure different hematological parameters like hemoglobin (Hb), white blood cells count, mean cell volume (MCV), mean cell hemoglobin concentration (MCHC) and packed cell volume (PCV). Serum (S) was used to evaluate renal biomarkers like creatinine, uric acid, urea and liver function test like aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin, albumin and lipid profile. Histopathology was done to evaluate drug-induced necrosis, fibrosis and cell damage at organ level (Yehya *et al.*, 2019).

STATISTICAL ANALYSIS

Data was represented as mean, average, standard deviation and ANOVA (one-way) using Microsoft Excel 2010.

RESULTS

Bulk and tapped density (table 2) are in the range of 0.21 g/mL ± 0.001- 0.22 g/mL ± 0.002. Carr's index has range of 9.7 ± 0.002-15.8 ± 0.001 for all formulations. In table 3, weight variation test for all formulation is 146.4 mg ±

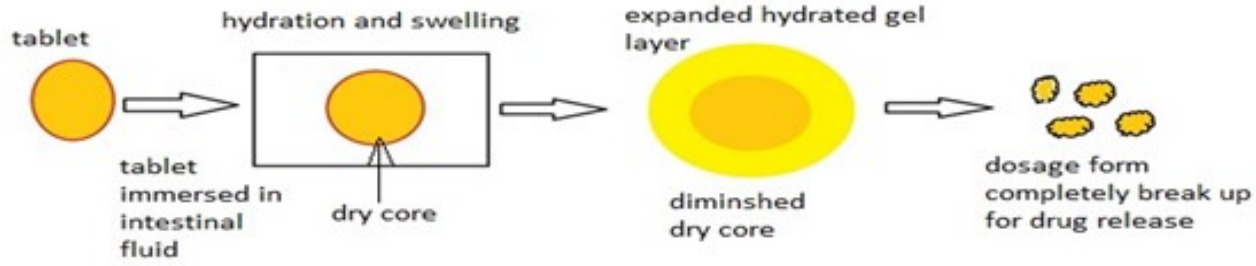

Fig. 1: Schematic representation of drug release from matrix tablet

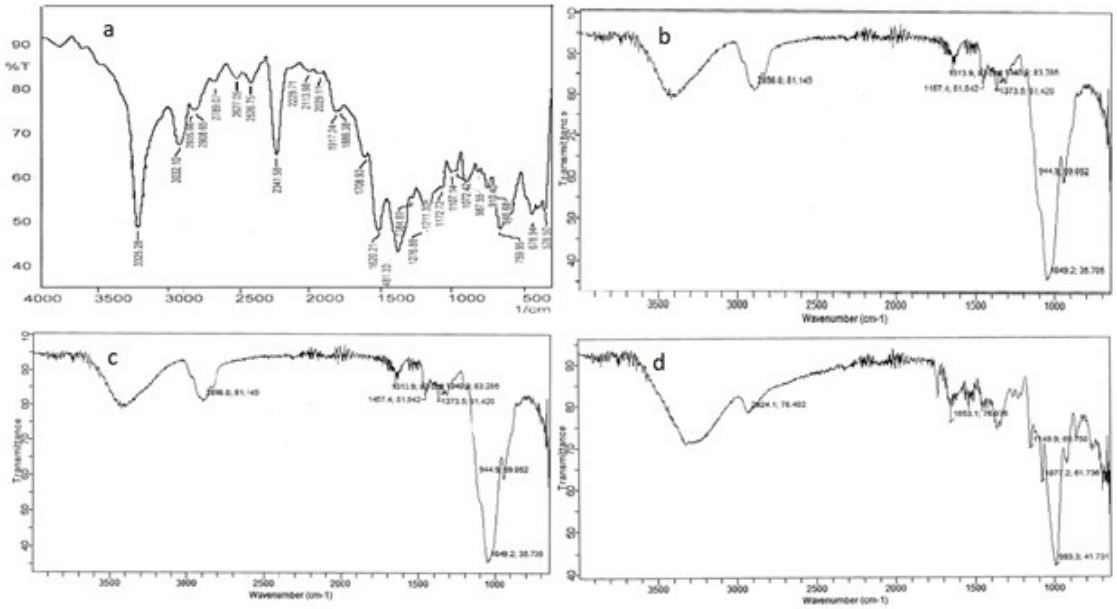

Fig. 2: FTIR of a) drug b) HPMC K100 c) physical mixture d) tablet

Table 1: Directly compressed matrix tablet

Ingredients	All ingredients were taken in mg				
	M1	M2	M3	M4	M5
Drug	12.5	12.5	12.5	12.5	12.5
HPMC K100	22	44	66	88	110
Micro Crystalline Cellulose	111.5	89.5	67.5	45.5	23.5
Magnesium stearate	2	2	2	2	2
Talc	2	2	2	2	2

Note: Five different batches of matrix tablets were prepared using different concentrations of polymer.

Table 2: Pre-compression parameter of directly compressed tablets

Formulation	Bulk density (g/mL) Mean ± S.D	Tapped density (g/mL) Mean ± S.D	Carr's Index Mean ± S.D	Hausner ratio Mean ± S.D	Angle of repose (θ) Mean ± S.D
M1	0.22± 0.005	0.25±0.005	15.8±0.001	1.2±0.009	19.9± 0.003
M2	0.21± 0.002	0.25±0.006	12.7± 0.003	1.2±0.003	19.7±0.003
M3	0.21± 0.002	0.24±0.002	13.8 ±0.003	1.2±0.003	18.97±0.009
M4	0.22±0.001	0.24±0.002	9.7± 0.002	1.10±0.003	19.99±0.003
M5	0.22±0.001	0.25±0	13.1 ±0.003	1.2±0.003	18.85±0.003

Table 3: Post-compression parameters of directly compressed tablets

Formulation	Weight Variation[1](mg) Mean± S.D	Friability[2](%) Mean± S.D	Thickness[3](mm) Mean ± S.D	Hardness[4] (kg/cm^2) Mean ± S.D	Assay[5](%) Mean ± S.D
M1	150±.03	0.06±0.66	7.9±.07	12.9±.01	99.99±0.03
M2	146.4±.35	0.06±0.65	8±0.04	13.05±.01	99.97±0.03
M3	154.1±.11	0.19±0.56	8.1±.02	10.7±.05	98.97±.0.5
M4	151.5±.24	0.19±0.56	8.8±0.5	10.86±.008	96.08±0.06
M5	151.3±.57	0.46±0.3	7.9±0.8	12.89±004	98.06±.0.02

0.35 to 154.1 mg ± 0.24. Friability range is 0.06% ± 0.66 to 0.46% ± 0.3 for matrix tablet. Values for thickness and hardness are 7.9 mm ± 0.07 to 8.8 mm ± 0.05 and 10.7 kg/cm^2 ± 0.05 to 13.05 kg/cm^2 ± 0.01 respectively.

DISCUSSION

FTIR spectra of drug, HPMC K100, physical mixture and tablet shown in fig. 2(a–d). FTIR spectra of drug (fig. 2a) showed narrow peaks at 3325.28 cm^{-1}, may be due to secondary amine showing medium NH stretching behavior. Absorption peaks above 3000 cm^{-1} are diagnostic of unsaturation. Weak but broad peak indicates presence of OH bond stretching at 3032.10 cm^{-1} to 2627.05 cm^{-1}. N-H stretching overlaps OH stretching vibration. Presence of weak thiol group is depicted by a characteristic peak at 2526.75 cm^{-1} followed by strong stretching of O=C=O at 2341.58 cm^{-1}. FTIR spectra also showed characteristic peaks of acetonitrile; strong but broad stretching peaks for isocyanate, strong stretching peaks of conjugated dimer acid, strong stretching peaks of aromatic ethers, esters. Unsaturated ketones are also observed in spectroscopy of drug.

FTIR spectra (fig. 2b) of HPMC K100 showed broad absorption and stretching peaks of OH group being overlapped by narrow peak of nitro group. A sharp narrow peak of anhydride is apparent at 1049.2 cm^{-1}. Bands for C=O are also visible in IR study of polymer (Lazzari *et al.*, 2018; Djerboua, 2019).

FTIR spectra of tablets (fig. 2d) exhibit strong broad peak of amine salt with stretching followed by C=C alkene group. Strong stretching peaks due to the carbonyl group of ether and primary alcohol are apparently followed by strong bending peaks of alkenyl group. Peak shifting and overlapping were not observed in FTIR study of formulation indicating that the drug and polymer are compatible.

TGA thermogram (fig. 3a-d) of drug, polymer, physical mixture and formulation showed three phase mass loss at different ranges of temperature when heated for testing. Initial mass loss is associated with water loss followed by second mass loss, proceeding further with third mass loss. DSC studies (fig. 4a-d) showed the drug has endothermic peaks at 370.51°C. Endothermic peaks of the drug were maintained at 368.44°C in M5 without any shift in position; indicating no interaction between the drug and selected polymers (Djerboua, 2019).

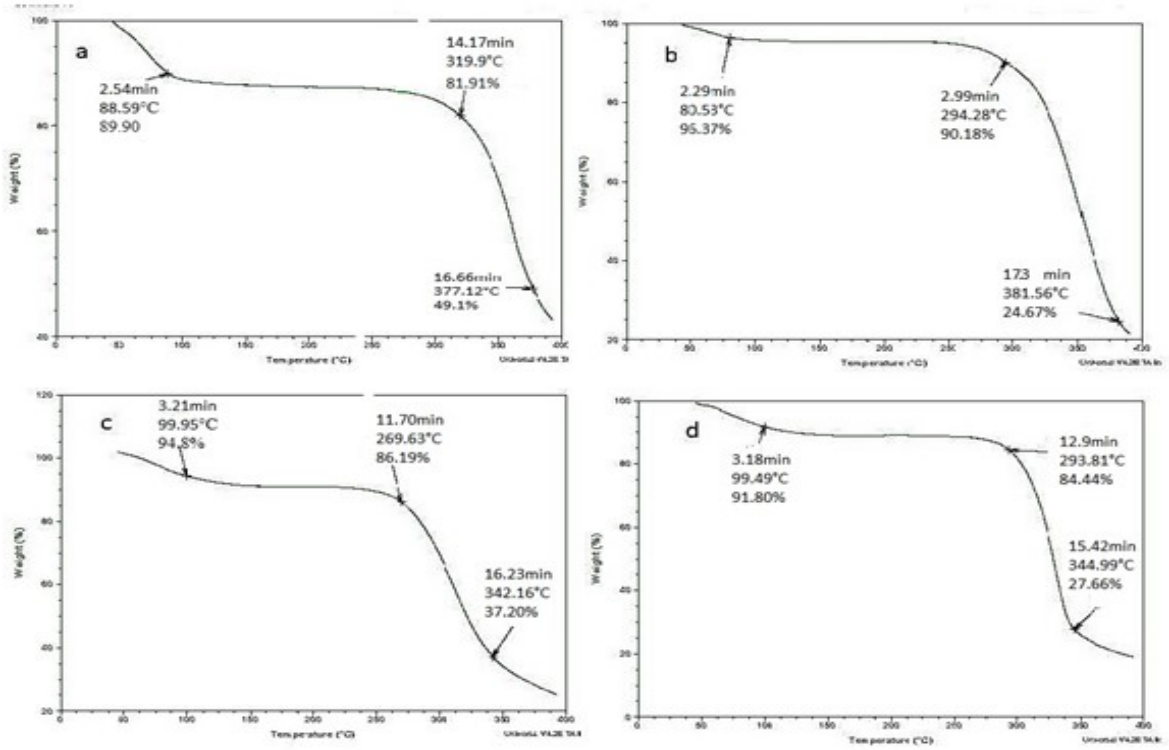

Fig. 3: TGA of a) drug b) HPMC K100 c) physical mixture d) tablet

Table 4: Similarity factor for matrix tablets

Formulation	M1	M2	M3	M4	M5
f_2 value	98.69	98.94	82.17	82.17	88.17

Table 5: Body weight of mice

Groups	Average of body weights (gram) Mean ± S.E.M		
	Day 1	Day 7	Day 14
Control	174.5±3.3	174.3±3.5	174.3±3.5
Test	173.7±8.5	173.7±8.5	173.7±8.5

Table 6: Organ weight of mice

Groups	Average of body weights of organ (gram) Mean ± S.E.M			
	Liver	Spleen	Kidney	P value
Control	45.5±0.04	2.2±0.004	19.6±0.02	Ns
Test	44.6±0.02	2.3±0.008	18.4±0.03	Ns

Note: Data is expressed as average and standard error mean. (p value< 0.05). ANOVA shows non-significance between all groups. Ns=non-significant

XRD plot (fig. 5-a) of drug lacks sharp peaks, showing it has amorphous structure. Similarly, XRD plot fig. 5(b-e) of HPMC K100, starch, physical mixture and tablet has no sharp peaks, revealing lack of crystallinity. The drug's amorphous structure remained intact in compressed tablet (Zhao and Augsburger, 2005; Djerboua, 2019). SEM study (fig. 7) declared that tablets possessed a uniform structure. They showed no cracks and non-homogenous structure (Zhang *et al.,* 2017).

Powder blend for all formulations has good to excellent flow properties. Hausner ratio has excellent and good properties. All results were in acceptable limits described in U.S.P. (Maheshwari *et al.*, 2018). Angle of repose has excellent flow properties from M1-M5.

Calculated range of weight variation test for compressed tablets is 163.3 to136.7 mg, implying that not a single tablet was beyond the limit of test range. Friability range is 0.06 ± 0.66 to 0.46% ± 0.3 for matrix tablet; no

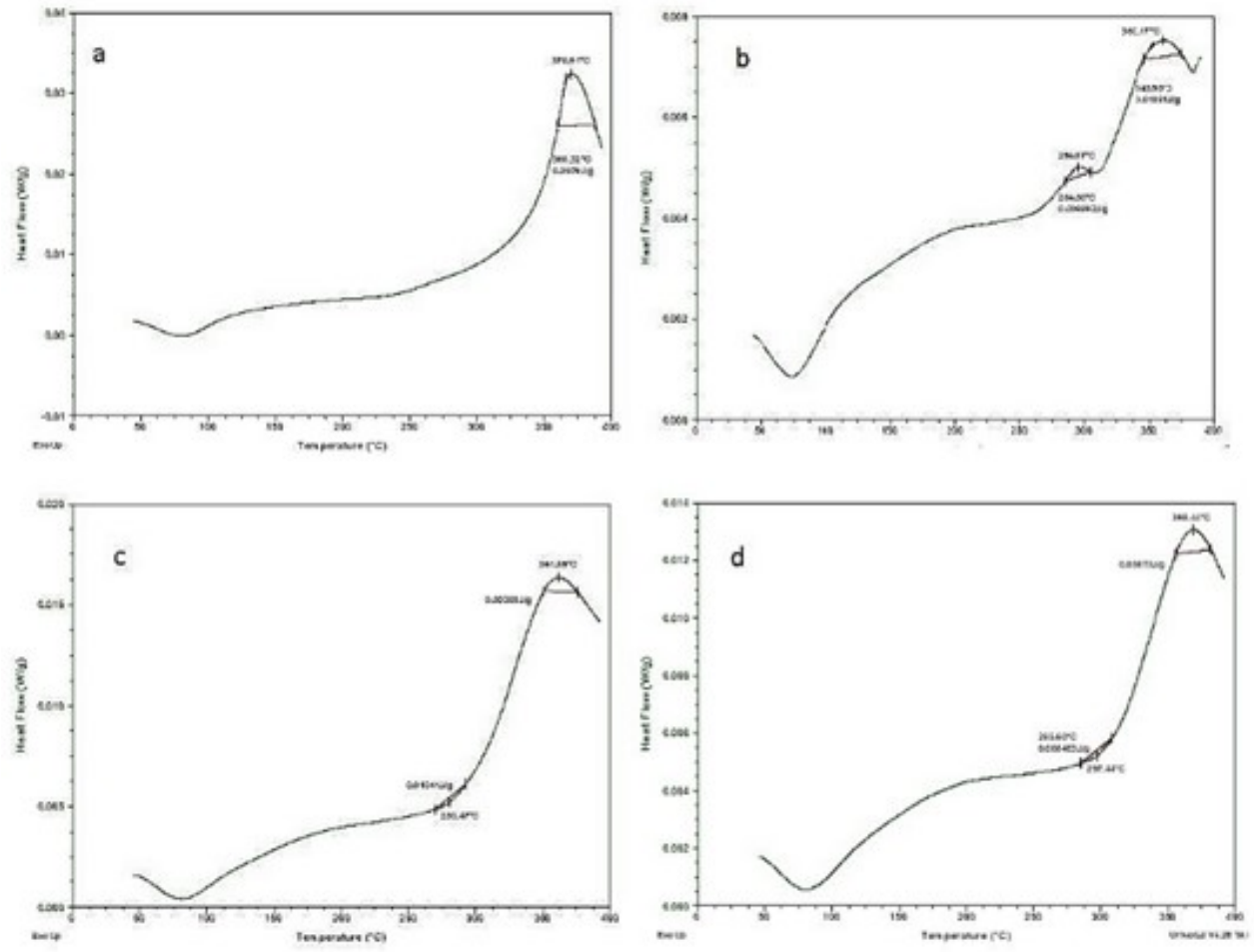

Fig. 4: DSC of a) drug b) HPMC K100 c) physical mixture d) tablet

Table 7: CBC analysis of control and test groups

Groups	Hemoglobin g/dL	T L C 109L	Total RBC 1012L	M C V FL	M C H pg	Platelets 109L
Control Average ± S.D	15.15±0.7	14.6±6.3	7.24±0.4	70.45±1.3	20.9±0.2	554±105.1
Test Average ±SD	15.4±1.0	8.85±0.8	8.85±0.8	72.6±1.0	21.95±0.4	624±92.0
Groups	M C H C %	HCT (PCV) %	Neutrophils %	Lymphyocytes %	Monocytes %	Eosinophils %
Control Average ± S.D	29.75±0.2	50.95±1.9	6±1.0	87.5±1.6	5±1.0	1.5±0.5
Test Average ±SD	30.25±0.1	50.9±3.2	4.5±0.5	90±2.1	4.5±1.6	1±0

Note: Data is represented as average and standard deviation

formulation showed friability greater than 1% meeting the pharmacopeia specification. Values for thickness and hardness and Assay are also in acceptable criteria (Moussa *et al*., 2019).

Dissolution profile (fig. 6) revealed the controlled release of the drug from the formulation; as polymer concentration increased gradually in M1 to M5, decreased drug release was observed. HPMC K100 is a synthetic

cellulose derivative possessing good retardant properties. Upon contact with water; it absorbs water, swells up and turns to gel-like mass. Dissolution media penetrates through the formed pores in the polymeric chain leading to diffusion of the drug from the matrix system and hence, promotes drug release (Zhang *et al.*, 2019). So, the difference in dissolution could be attributed to the difference in the matrix tablet composition. Similarity factor (table 4) calculated for matrix tablets using coated tablets of stablon as reference. It's value is greater than 50% for all matrix tablets (Huang *et al.*, 2018), indicating that design tablets were not different from the stablon.

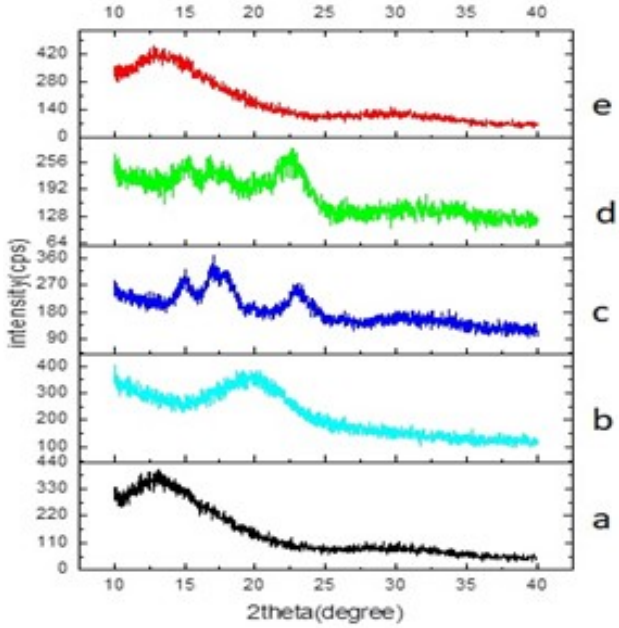

Fig. 5: XRD plot of a) drug b) HMPCK100 c) starch powder d) physical mixture e) tablets

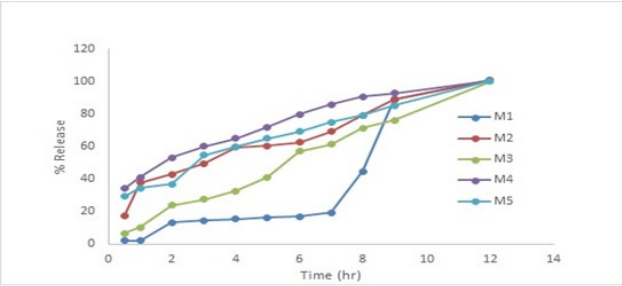

Fig. 6: Release profile of directly compressed matrix tablet

All parameters of physical activity were found to be normal after every dose administration in all mice of control and test groups. No change was observed in sensation, gate, movement, excretion and secretions. Matrix tablets did not affect the weight of animals and different organs (tables 5 and 6) in T group when compared to the C group (p value <0.5).

CBC analysis (table 7) showed no remarkable changes in the blood profile, meaning that drug has no blood dyscrasias ability, as many anti-depressants and chemotherapeutic agents showed blood dyscrasias; a major side effect (Yehya *et al.*, 2019).

Liver function tests (table 8) of T group were in normal range. A minor rise in AST and alkaline phosphatase was reported, which was not significant. Renal biomarkers (table 9) were also normal for T group. Lipid profile (table 9) was in the normal range, indicating that the drug did not affect the liver and renal function and hence, it is not hepato and neprhro toxic (Yehya *et al.*, 2019; Mahmood *et al.*, 2016). Histopathological data (fig. 8) indicated no sign of necrosis, steatosis and fatty liver at organ level. No signs for hypoxia were observed in cardiac cells. Acute toxicity study of tianeptine tablets in mice is still unreported in literature.

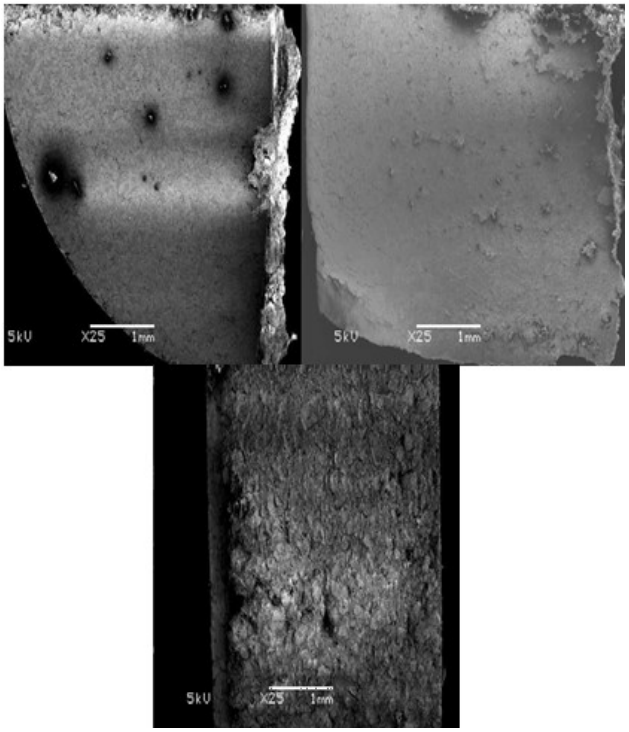

Fig. 7: SEM of matrix tablets

CONCLUSION

It was concluded that matrix tablets were prepared by direct compression method using HPMC K100 and tianeptine as model drug. Gelling nature of HPMC K100 retarded drug release and tablets exhibited extended release property. Acute toxicity study proved that compressed tablets are safe in animals, as no sign of toxicity was observed in organ physiology and histology. Hence, the dosage form will provide a new way for manufacturers to develop extended release dosage form.

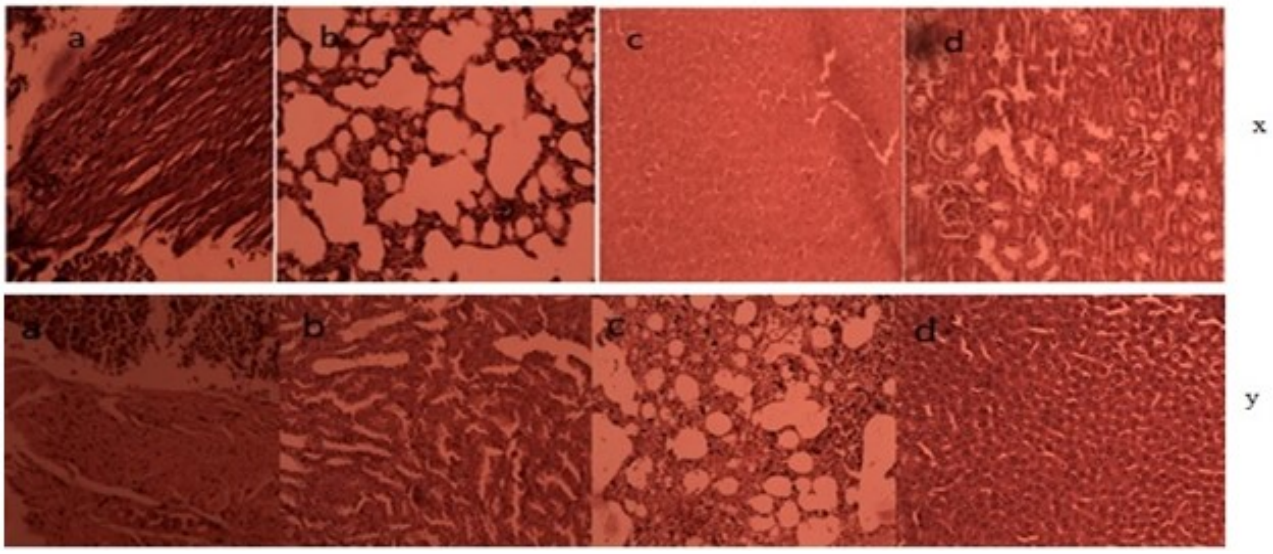

Fig. 8: Histopathological view of a) liver b) kidney c) heart d) lung of control (x) and test (y) group

Table 8: Biochemical profile of different parameters in control and test groups

Groups	S. bilirubin (Total) mg/dL	AST u/L	ALT u/L	ALP u/L
Control Average ± S.D	0.308 ±0.01	93.5±29.02	78.5±24.64	83.5±27.93
Test Average ± S.D	0.295±0.01	117.5±7.5	97±5	178±32

Note: Data is represented as average and standard deviation

Table 9: Renal function test and lipid profile of control and test groups

Groups	S. protein g/dL	S. albumin g/dL	Blood urea mg/dL	Blood urea nitrogen mg/dL	S. creatinine mg/dL	S. uric acid mg/dL
Control Average ± S.D	6.95±0.05	3.95±0.27	26.5±7.12	12±3.28	0.745±0.19	7.2±2.40
Test Average ± S.D	5.85±0.55	4.25±0.35	30.5±11.5	13.5±5.5	0.755±0.375	10.95±2.65
Groups	S. cholesterol mg/dL	S. triglycerides mg/dL	S. high density cholesterol mg/dL	S. low density cholesterol mg/dL	VLDL cholesterol mg/dL	-
Control Average ± S.D	91±3.28	127.5±10.40	31.5±2.73	69.5±3.834058	25±2.19089	-
Test Average ± S.D	106.5±20.5	119±23	31.5±4.5	67±2	23.5±4.5	-

Note: Data is represented as average and standard deviation. VLDL is very low density lipoprotein.

Currently no extended release product of tianeptine is available in market.

Controlled release formulation of the tianeptine sodium could be prepared by using the synthetic and natural polymers. Moreover, bioequivalence, bioavailability and *invivo* studies could be performed on these design tablets.

Dose dumping; common drawback of the sustained release system may happen with the design dosage form.

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