

<https://doi.org/10.56770/jcp2025912>

FAST RELEASE FORMULATION OF TIANEPTINE SODIUM: FORMULATION, DESIGN, CHARACTERIZATION AND TOXICITY STUDY

Nabila Abdus Salam¹, Muhammad Riaz^{1,2}, Liaqat Ali^{1*} 

¹ Faculty of Pharmaceutical Sciences, Government College University Faisalabad, Pakistan

² School of Pharmaceutical Sciences, Universiti Sains Malaysia, Malaysia

³ Drug Inspector, Health Department, Government of Punjab, Pakistan.

Submitted: July 12, 2024; Revised: January 28, 2025; Accepted: February 17, 2025; Published: June 30, 2025

ABSTRACT

Background: Tianeptine sodium is an antidepressant drug possessing analgesic and anti-asthmatic property. Orodispersible tablets rapidly disintegrate with in oral cavity and drug undergoes rapid absorption through oral mucosa resulting in rapid therapeutic effect. The objective of present study was development and characterization of the fast release tablets of tianeptine sodium in order to target the population with inflammatory bowel disease as it is more prevailing disorder. **Method:** Fast release tablets prepared by direct compression method and evaluated for pre and post compression parameters. Cross povidone is most superior to cross carmellose sodium and sodium starch glycolate as a disintegrating agent. Combination of cross povidone and cross carmellose resulted in gel like mass; prolonging the disintegration time of formulation and retarding the release of drug from formulation. **Results:** Drug release showed that cross povidone provided the good release profile as compared to the other superdisintegrants. Superdisintegrant concentration is also a rate limiting step for disintegration time. FTIR, DSC, TGA and XRD studies showed compatibility, thermal stability and amorphous nature of the samples used in study. Acute toxicity study conducted on swiss albino mice showed that that developed dosage form is nontoxic as no changes in physical activity and function of organs was observed. Histopathological study revealed that developed dosage form did not develop any kind of necrotic changes indicating the safety of dosage form. **Conclusion:** Fast release tablets of tianeptine sodium could be developed by direct compression method using the different concentration of superdisintegrants. Directly compressed tablet were safe for use in animal as administered tablets did not show any toxicity at organ level.

Keywords: Tianeptine sodium, Disintegration time, Cross povidone, Sodium starch glycolate, Cross carmellose sodium.

*Corresponding Author. E-mail: liaqat_srp@hotmail.com

INTRODUCTION

Inflammatory bowel disease (IBS) is most common inflammatory disorder of bowel characterized by abdominal pain, discomfort, bloating, defecation and constipation [1]. IBS is painful disorder of GIT that affects both men and women prevailing from Asia to United State [2, 3]. IBS is a relapsing disorder that with the passage of time may improve, unchanged or even worsen. It may quality of life and productivity [4].

Antidepressants are widely used for the treatment of depressive disorder but they have proven antinociceptive activity. They are true analgesic and effective for the treatment of IBS even with coexisting psychological disorder: as compared to other analgesic the exact mechanism of action is least known but their analgesic activity is well established in different clinical and experimental

studies. They have effect on pain perception that's why prescribed for abdominal pain associated with the IBS [5, 6].

Owing to ease of administration oral route is most preferable leading to enhanced patient compliance. Among the available oral dosage form tablets are most preferable dosage form because it more stable as compared to liquid dosage form and capsules due to more temper proof capability [7]. Orodispersible drug delivery system includes films and tablets that rapidly disintegrates in buccal cavity within 60 seconds of administration [8]. Orally disintegrating tablets broaden the use of medicine in case of dysphagia, motion sickness, acute depression, pain and other medical emergencies. Drug absorption through the mucosal membrane facilitate the rapid therapeutic effect [9].



Use of superdisintegrants facilitate the rapid disintegration of tablets with in mouth. They may be from natural or synthetic source. Commonly used and easily available disintegrants includes MCC, cross povidone, starch, sodium starch glycolate, cross carmellose, xanthan gum, maltose powder and isapgghula husk. Choice of superdisintegrant is based on the nature of ingredients, compression method and drug candidate for the particular formulation. Disintegration process depends on the porosity, hydration and size distribution. Porosity is a pathway for water penetration into tablet enhancing drug dissolution possible mechanism of disintegration is swelling, wicking, repulsive forces between the disintegrating particles and deformation which totally depends upon the nature of selected polymers [10]. Sodium starch glycolate has good swelling capacity and allow the penetration of water even in the presence of hydrophobic excipients. Cross povidone is preferred because of good compressibility, high wicking capability and little tendency to form gel like mass when compared to sodium starch Glycolate. Cross carmellose is a modified cellulose that having disintegrating tendency when added to mouth dissolving tablets [11].

Tianeptine sodium (TS) is a novel modified tricyclic antidepressant that is used for the treatment of drug resistant depression, asthma, anxiety and pain [12]; while comparing to other tricyclic antidepressant TS has least side effects with less drug dependence. Drug is available as white powder turns to yellowish wax like solid upon absorption of water, very soluble in dichloromethane. Drug is available under the brand name of Stablon as coated tablet, coaxial, tatinol prescribed for the major depression, post-traumatic stress disorder anxiety, pain and inflammatory bowel disease. In GIT serotonin level is major player in controlling the digestive activity and intestinal secretion being altered in IBS leading to inflammation and pain in bowel. This increased serotonin level is reduced by using the TS thus improving the symptoms of IBS.

The objective of present study is formulation and characterization of the novel fast release tablet of

TS for the treatment of abdominal pain in IBS. The significance of this study is that currently no fast release formulation of TS is available in market. These fast release tablets will provide the quick relief from the abdominal pain in IBS and also reduce the serotonin level through inhibitory mechanism in GIT which is the leading cause of abdominal pain due to its effect on intestinal secretions.

EXPERIMENTAL

Materials

TS gifted from Servier Pharmaceuticals Lahore Pakistan. Sodium Starch Glycolate (SSG), Cross Povidone (CP) and Cross Carmellose Sodium (CS) were gifted from Stand Pharma (Pvt) Ltd Pakistan. Starch and Microcrystalline Cellulose was purchased from the Daejung, Korea. Talc and Magnesium Stearate was purchased from Sigma Aldrich, Germany. Distilled water using Stuart water distillation unit (EW 99295-0X United Kingdom) was prepared in Lab 5 of department.

Preparation of Fast Release Tablets

All ingredients weight individually and pass through the sieve no 60 followed by another sieving and mixed in pestle and mortar for 15 min. After mixing; powder blend was lubricated using magnesium stearate and talc and mixed well for additional 30 min. Mixed powder was subjected to compression using rotary die machine ZP-19. Finally, tablets were prepared having the different concentration of superdisintegrants (Table 1).

Precompression Parameter

After weighing all ingredients powder blend was evaluated for the precompression parameters; Bulk Density, Tapped Density, Hausner's Ratio, Angle of Repose [13, 14]. FTIR, DSC, TGA and XRD conducted for the drug, polymers, physical mixture and compressed tablets.

Fourier Transformed Infrared Spectrophotometry

FTIR (IR Affinity-1, Shimadzu, Kyoto, Japan) study was done to find out the drug and polymer incompatibilities. Sample was analyzed in solid state using KBr disc at 4000-400 cm^{-1} under 150 kg/cm hydraulic pressure. FTIR results were compared with the table of standard values [15].

Table 1: Preparation of fast release tablets of TS.

Formulation	Drug (mg)	CS (mg)	SSG (mg)	CP (mg)	Starch (mg)	MCC (mg)	MS (mg)	Talc (mg)	Aspartame (mg)
OD1	12.5	60			20	51.5	2	2	2
OD2	12.5	70				41.5	2	2	2
OD3	12.5	80			20	31.5	2	2	2
OD4	12.5		60		20	51.5	2	2	2
OD5	12.5		70		20	41.5	2	2	2
OD6	12.5		80		20	31.5	2	2	2
OD7	12.5			60	20	51.5	2	2	2
OD8	12.5			70	20	41.5	2	2	2
OD9	12.5			80	20	31.5	2	2	2

MCC= Microcrystalline cellulose, SSG = Sodium Starch Glycolate, CP = Cross Povidone, CS= Cross Carmellose Sodium, MS= Magnesium Stearate

Differential Scanning Calorimetric Analysis

DSC (DSC-60, Shimadzu, Kyoto, Japan) analysis performed to evaluate crystallinity and amorphous nature of drug, physical mixture and formulation at high temperature under nitrogen flow. DSC; a thermolytic process using 2-4 mg of sample heated in an aluminum pan at 20-250 °C being scanned at 20 °C/min [16].

Thermogravimetric Analysis

TGA (TGA-60, Shimadzu, Kyoto, Japan) conducted to check the thermal stability of drug, physical mixture and tablet. All samples were tested at 25-600 °C along with heating rate of 20 °C/min in the presence of nitrogen gas flow.

X-RAY Diffraction

XRD (PANalytical Empyrean, Almelo, The Netherlands) carried out to determine the crystalline structure of drug, polymers and formulation. Sample were run using Cu-K α radiation at 2 θ =5-30°. XRD pattern was plotted using Origin Pro software.

Bulk and Tapped Density

Bulk and tapped density was measured by cylinder method. 2g of powder was taken in volumetric cylinder and initial volume of cylinder was noted. Cylinder was tapped on smooth surface at height of 2.5 cm. Tapping was continued till the volume became constant. TBD and LBD was calculated for every formulation in triplicate.

Compressibility Index

Compressibility index was determined to evaluate the flow properties of powder blend. Each parameter measured in triplicate.

Post-compression Parameters

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

Thickness and Hardness

Monsanto hardness tester (PX/THT-3957) was used to measure thickness and hardness. Hardness provides information about the breaking point and structural integrity of tablets under the force. 10 tablets were taken individually and placed diagonally between the jaws of machine to measure thickness and hardness.

Friability

Friability also describes the shock absorbing capability of tablets during the handling, shipment and transportation before use. 20 tablets were taken in Roche friabilator and average weight was measured, tablets were placed inside the drum which rotates at 25 rpm. Tablets fell downward in drum underwent the abrasion and removed, dedusted and percentage weight loss calculated by following formula. Friability must be ≤ 1 .

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

Weight Variation Test

Weight variation test was carried out to calculate the variation in weight of tablets. 20 tablets taken

and individually weighted. Average of tablets calculated and variation in weight calculated by comparing the individual weight with the average weight of tablet.

$$\% \text{age weight variation} = \frac{(\text{individual weight} - \text{average weight})}{(\text{average weight})} * 100$$

The tablets meet the USP test if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. The weight variation tolerances for uncoated tablets differ depending on average tablet weight.

Disintegration Time

DT was determined using two station disintegration tester (Toron Pharma – DT2AL North America). 900 mL of phosphate buffer were maintained at 37 $\pm$ 0.5 °C. Randomly selected six tablets were placed individually in racks inside the basket immersed in disintegration media containing beakers and time taken by tablets to disintegrate was noted.

Wetting Time

Wetting time was measured by petridish method. Filter paper of 10 cm was placed inside the petridish. 1mL of water containing methylene blue was added to this petridish, tablet was placed carefully on it and wetting time of tablet was measured using stop watch. Test was performed on 5 tablets for each formulation [17].

Content Uniformity

Content uniformity means uniform distribution of all particles in dosage form. For this test, take 5 tablets taken, crushed in pestle and mortar to obtain a finely divided powder followed by sieving. An equivalent weight to a single tablet of prepared powder taken to prepare the solution with a miscible solvent. Prepared solution was then filtered and run on UV spectrophotometer at 254 nm for absorbance. It's range must be 95-110% with relative standard deviation equal or less than 6%.

Dissolution Study

Dissolution study was carried out in order to determine the release of drug from formulation. Dissolution studies were conducted in USP type II apparatus (Pharma test Germany). 900 mL of phosphate buffer pH 6.8 employed in each vessel and speed of rotation was 50 rpm. 5 mL of sample was removed at specific time intervals (10, 20, 30, 40, 50, 60 min), withdrawn volume was replaced with the freshly prepared phosphate buffer and sample was analyzed on UV spectrophotometer (Shimadzu Japan) at 254 nm. Dissolution studies performed in triplicate.

Stability Studies

Stability studies were conducted according to International Conference on Harmonization (ICH) guidelines for 90 days and selected formulation was evaluated for physical appearance, wetting time, friability and drug content on 30, 60 and 90 day [18].

Toxicity Studies

Toxicity studies were conducted according to Organization for Economic Cooperation and Development (OECD) guidelines in accordance with the standard protocol set by “Pharmacy Research Ethics Committee” of Faculty of Pharmaceutical Sciences Govt. College University Faisalabad Punjab, Pakistan (Ref.No. GCUF/ERD/1764 dated 10-10-2017). Animals were properly handled in accordance to good agreement with UK Animals Act 1986 for scientific procedure. Swiss albino mice were divided into two groups (n-6) i.e. control and test

group. Mice were evaluated physically, food and water intake, mobility and any kind of alignment; having free access to food and water in cage. Dose calculation was done for the optimum formulation according to OECD guidelines higher than the therapeutic dose of TS. Mice were provided with autoclaved food and water and kept fast overnight prior to dose administration having free access to water. Calculated dose was dissolved in distilled water using the vortex mixing to form suspension. Controlled group was administered with distilled water 1 mL/kg. Test group was administered with dose 25mg/kg using gastric gavage.



Figure 1: Drug administration process a) animal in cage b) drug suspension for dosing c) dose.

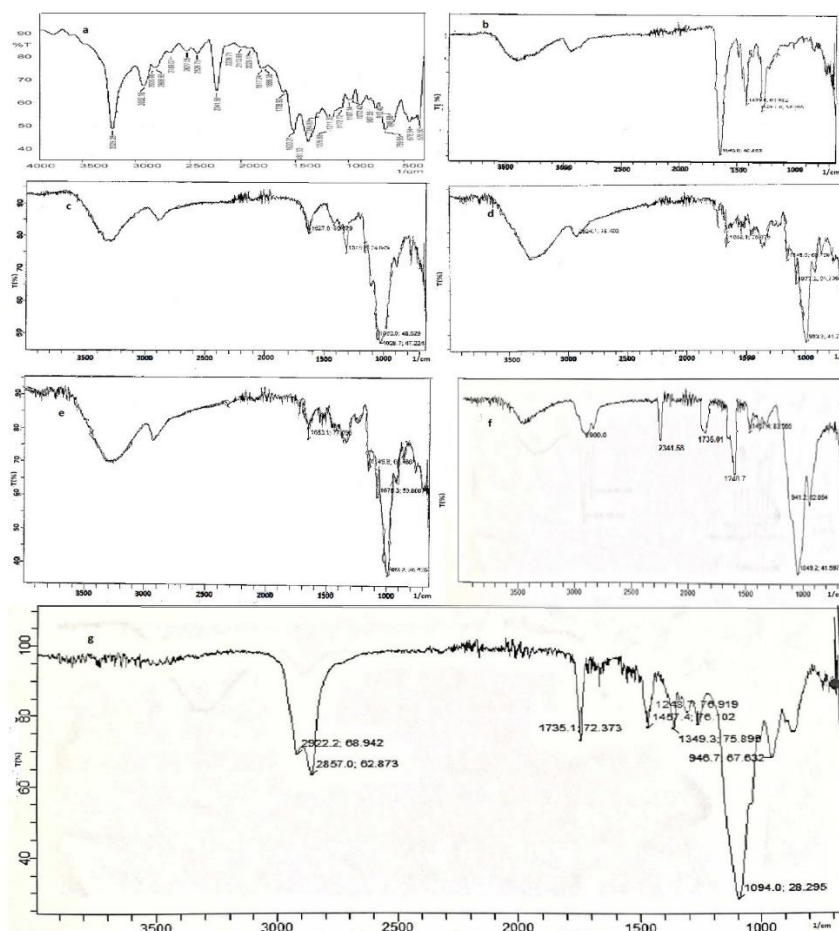


Figure 2: FTIR spectra; drug (a) cross povidone (b) cross carmellose (c) sodium starch glycolate (d) physical mixture (e) and tablet (f).

Table 2: Precompression parameter of powder blend for fast release tablets.

Formulation	Bulk density	Tapped density	Compressibility index	Hausner ratio	Angle of repose
OD1	0.22±0.004	0.25±0.004	10.87±0.009	1.13±0.009	17.63±0.00
OD2	0.21±0.002	0.25±0.006	14.89±0.003	1.18±0.003	16.97±0.15
OD3	0.21±0.002	0.25±0.002	13.69±0.003	1.16±0.003	16.11±0.28
OD4	0.22±0.001	0.24±0.002	9.78±0.003	1.11±0.002	17.29±0.15
OD5	0.22±0.002	0.25±0	13.97±0.003	1.16±0.003	18.06±0.16
OD6	0.21±0.003	0.24±0.002	11.58±0.006	1.13±0.006	17.64±0.32
OD7	0.21±0.002	0.24±0.002	13.68±0.003	1.16±0.003	16.76±0.15
OD8	0.21±0.002	0.24±0.002	10.64±0.003	1.12±0.002	18.41±0.006
OD9	0.21±0.002	0.24±0.004	11.58±0.002	1.14±0.003	18.41±0.006

After dose administration animals were observed for the changes in skin, gait, activity, salivation, urination, diarrhea, lacrimal secretion, sedation, body weight, food and water consumption for 14 days. On 14th day blood samples were collected for hematological and biochemical analysis from each mice in controlled and test group. Animals were sacrificed and their vital organs were preserved in formalin (10%) solution for the histopathological examination.

RESULTS AND DISCUSSION

Precompression Parameters

Value of compressibility index for OD1, OD4, OD8 have excellent flow property OD2 and OD3, OD5, OD6, OD7, OD9 has good flow property. Values of HR for OD1, OD2, OD3, OD5, OD6, OD7, OD8 and OD9 are good flow properties, OD4 excellent (Table 2).

FTIR spectra of drug, cross povidone, cross carmellose, sodium starch glycolate, starch, physical mixture and tablet is shown in figure 2 (a-g). FTIR spectra of drug showed narrow peaks at 3325.28 cm⁻¹ which may be due to the secondary amine having medium NH stretching behavior. Absorption peaks above 3000 cm⁻¹ are diagnostic of unsaturation. Weak but broad peak indicates the presence of OH bond exhibiting OH stretching at 3032.10 cm⁻¹ to 2627.05 cm⁻¹. N-H stretching is overlapped by the OH stretching vibration. The 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 of drug also showed the characteristic peaks of acetonitrile, strong but broad stretching peaks for isocyanate, conjugated dimer acid, aromatic ethers, esters and peaks for the unsaturated ketones are also observed.

FTIR spectra of cross povidone showed the medium stretching due to C-H group which may contribute to the alkane group followed by appearance of new peak of aldehyde group with medium C-H stretching. A fairly strong stretching of conjugated aldehyde at 1735.1 cm⁻¹ is possibility due to carbonyl group being overlapped by bended peak at 1457.4-1349.3 cm⁻¹. This ending is due to presence of methyl and methylene group in sample. A characteristic peak of secondary alcohol with strong stretching character is visible at 1094.0 cm⁻¹.

FTIR spectra of cross carmellose exhibit strong broad peak of amine salt with stretching followed by the C=C alkene group. Strong stretching peaks due to the carbonyl group of ether and primary alcohol is apparent followed by the strong bending peaks of alkenyl group.

FTIR of starch powder depicts the broad peaks which are due to the N-H stretching vibration overlapped by absorption peaks at 1464.8 cm⁻¹. C-O stretching due to tertiary alcohol vibrations was also observed at 1049 cm⁻¹. FTIR spectra of SSG showed the broad absorption peaks with stretching which is overlapped by narrow peak of nitro group. A sharp narrow peak of anhydride is apparent at 1049.2 cm⁻¹. FTIR of physical mixture with characteristics peaks at 2900, 1457.4 and 941.2 cm⁻¹ are due to amine, alkyne and alkene. Absorption peak at 2950-2850 cm⁻¹ is indication of lack of unsaturation. FTIR of Tablet showed the peaks at 2924.1, 1407.1, 1323.0 -1140.62, 1105.2 cm⁻¹ due the alcohol, nitro, aliphatic ether and secondary alcohol with strong stretching vibration. FTIR study showed lack of physical incompatibility between drug, polymers and compressed tablets as there is no change in characteristic peaks of functional groups for obtained spectra when compared.

DSC Thermogram (Fig. 3) showed lack of crystallization and presence of amorphous nature in tested samples. Appearance and disappearance of some peaks in DSC thermogram is indicative of physical interaction among the used polymers and drug.

TGA studies (Fig. 4) conducted to evaluate the mass change or weight loss and thermal stability of the drug, physical mixture and drug. TGA of drug showed three step degradation with mass loss at different temperature. After 2.64 min mass loss is 10.10 % at 88.59 °C, this initial mass loss was due to the water loss. At 319.98 °C mass loss is 18.09 % after 14.17 min followed by 51.90% mass loss at 377.12 °C after time lapse of 16.81 min; hence providing the evidence that drug is stable at high temperature. TGA thermogram of physical mixture showed three phase mass loss. It was observed that sample had 3.63 % mass loss when heated at 80.53 °C for 2.29 min due to water loss from the physical mixture in first phase. Second phase mass loss was

observed at 294.28 °C which is 9.82 % heated for 12.99 min. Third phase total mass loss is 75.33 % after heating for the 15.2 min at 342.15°C.TGA thermogram of OD tablet showed mass loss 5.72 %

at 3.21 min at 99.96 °C followed by second mass loss 13.81 % at 342.15 °C due to the initial dehydration of the dosage form. Further decrease in weight continued and last from 34.15 – 400 °C.

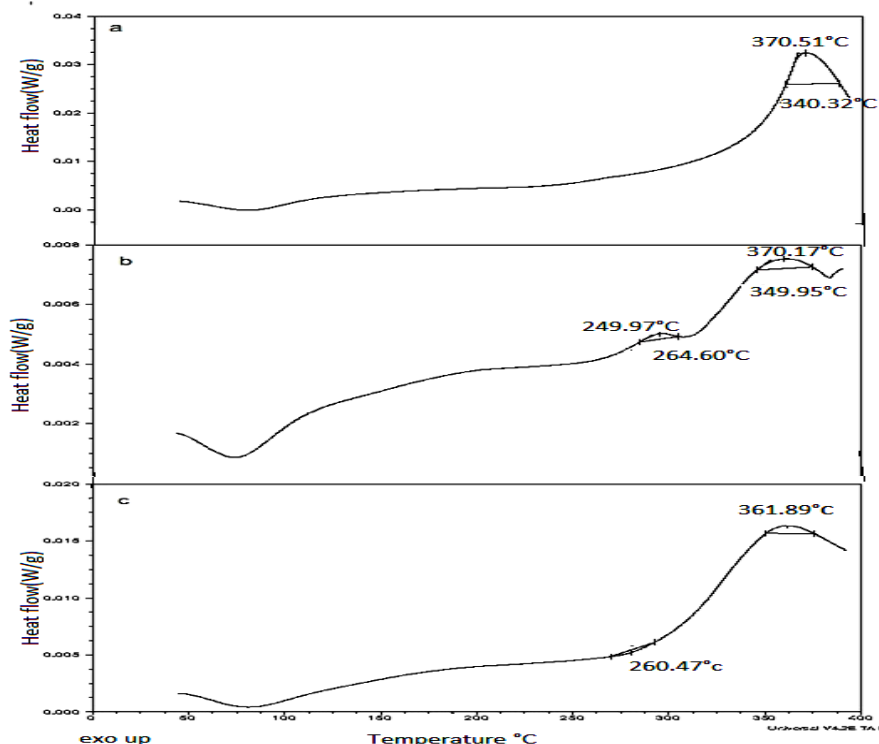


Figure 3: DSC Thermogram of drug (a) physical mixture (b) and tablet(c)

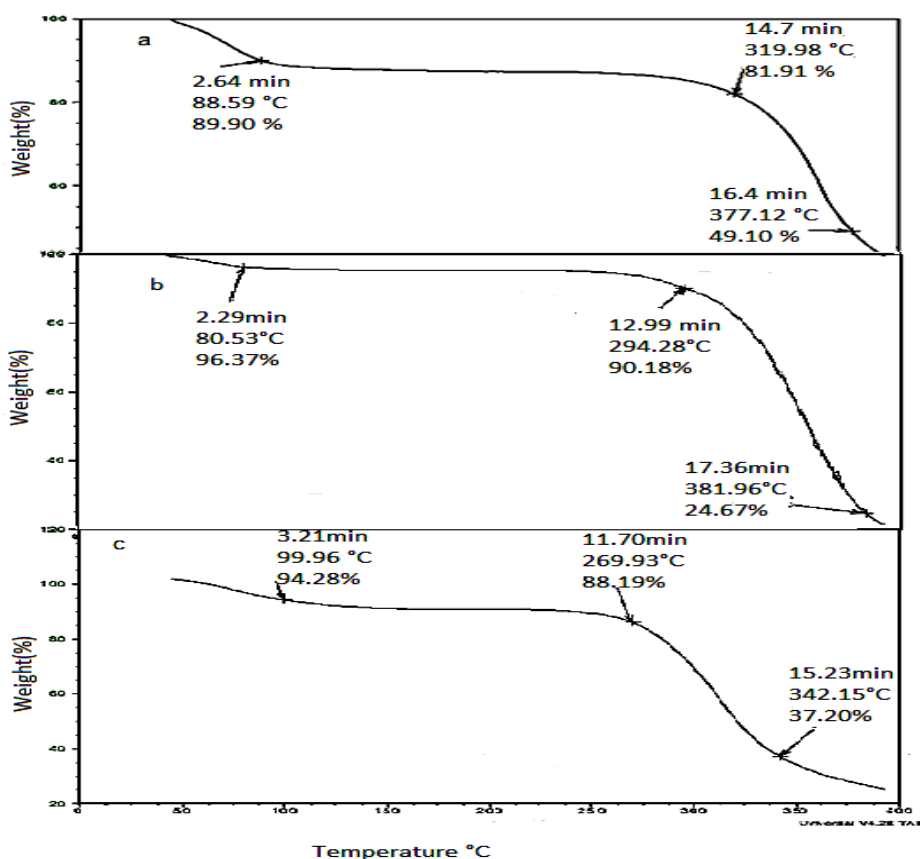


Figure 4: TGA Thermogram of drug (a) physical mixture (b) and tablet (c)

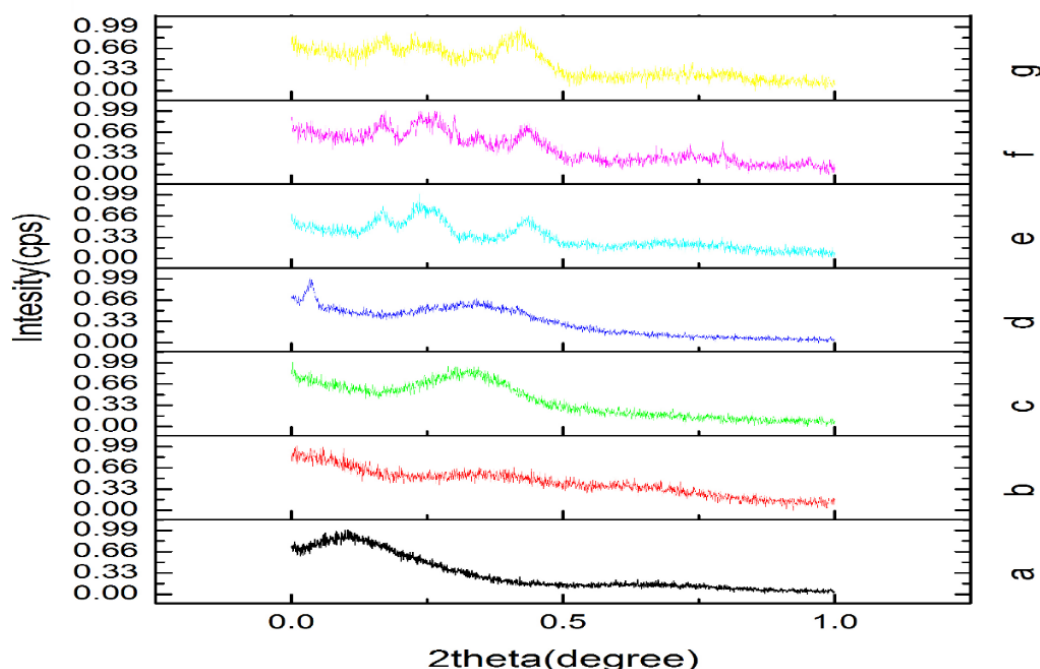


Figure 5: XRD pattern of drug (a) cross povidone (b) starch powder (c) sodium starch glycolate (d) cross carmellose (e) physical mixture (f) and fast release tablet (g).

Table 3: Post-compression parameters of directly compressed fast release tablets of TS.

Formulation	Weight Variation (mg) $\pm$ S.D n=20	Thickness (mm) $\pm$ SD n=10	Hardness (kgm/s ²) $\pm$ SD n=10	Friability $\pm$ SD n=20	Disintegration time (sec) n=6	Wetting time (sec) n=5	Assay $\pm$ S.D n=5
OD1	150.1 $\pm$ 0.03	7.9 $\pm$ 0.07	12.9 $\pm$ 0.01	0.06 $\pm$ 0.6	100	100 $\pm$ 0.89	99.99 $\pm$ 0.03
OD2	146.4 $\pm$ 0.4	8 $\pm$ 0.04	13.05 $\pm$ 0.01	0.06 $\pm$ 0.6	52	50.6 $\pm$ 1.14	99.97 $\pm$ 0.03
OD3	154.1 $\pm$ 0.11	8.1 $\pm$ 0.02	10.7 $\pm$ 0.05	0.19 $\pm$ 0.5	49	49.6 $\pm$ 0.49	98.97 $\pm$ 0.05
OD4	154.5 $\pm$ 0.3	8.8 $\pm$ 0.5	10.86 $\pm$ 0.08	0.19 $\pm$ 0.5	169	169.6 $\pm$ 0.55	96.08 $\pm$ 0.06
OD5	151.2 $\pm$ 0.6	7.9 $\pm$ 0.8	12.89 $\pm$ 0.04	0.46 $\pm$ 0.3	130	131 $\pm$ 0.71	98.06 $\pm$ 0.02
OD6	148.9 $\pm$ 0.15	8.1 $\pm$ 0.08	11.29 $\pm$ 0.04	0.30 $\pm$ 0.5	93	94.2 $\pm$ 0.84	98.06 $\pm$ 0.02
OD7	151.67 $\pm$ 0.4	8 $\pm$ 0.03	11.27 $\pm$ 0.04	0.58 $\pm$ 0.2	51	51.6 $\pm$ 0.55	99.98 $\pm$ 0.29
OD8	153.12 $\pm$ 0.3	8 $\pm$ 0.08	12.03 $\pm$ 0.02	0.19 $\pm$ 0.5	20	21.6 $\pm$ 1.34	99.99 $\pm$ 0.03
OD9	152.2 $\pm$ 0.12	8.1 $\pm$ 0.11	12.06 $\pm$ 0.02	0.65 $\pm$ 0.6	9	11 $\pm$ 1.23	96.02 $\pm$ 0.06

No sharp peaks were observed in obtained XRD pattern of all samples (figure 5a-g) indicates the amorphous nature of samples except physical mixture in which peak are going to appear although that peaks are not too sharp as for the crystalline sample [19].

Post-compression Parameters

Weight variation test for all the formulation has a range of and results are within the acceptable range. Friability of all formulation is within acceptable range that is less than 1%. Hardness value for all formulation is within 10.27-13.05 kgm/s². Value of assay is 96.02 $\pm$ 0.06-99.99 $\pm$ 0.03. DT is in range of 9 to 100 sec (Table 3).

This study also revealed that DT is inversely proportional to concentration of superdisintegrants. The starting concentration for all above mentioned polymers was 4mg which was gradually raised to 8, 12 mg [20] and observed DT was at this concentration was greater than one hour and whole

tablet disintegrated after 300 min; being too high than reported in literature. The second concentration of all above mentioned superdisintegrant was 15, 30, 45 mg [21] and observed DT for all these concentrations for 120 min. Again a third trial was performed by selecting the new concentration of polymers which is 60, 70, 80 mg and observed DT at these concentration was in range of 9-169 seconds.

Combinations of superdisintegrants were also used at various concentrations. It was observed that the combination of CP and SSG give gel like structure when come into contact water as SSG slowly swells in water.

Superdisintegrant concentration also affects the DT as more the concentration of polymers less is DT. Among the all the selected superdisintegrant; cross povidone gives the least DT at the same concentration of cross carmellose and sodium starch glycolate. Between the cross carmellose and

sodium starch glycolate DT is less for the former related to its structure. It possesses fiber like structure which act as hydrophilic pores to absorb water from the dissolution media and promote the breakup of large particles to small one. CS is superior to the sodium starch glycolate that give gel like mass which is due to its spherical structure. This type of structure retains the water and swell slowly on contact with water. DT is higher for sodium starch glycolate as compared to cross carmellose. Cross povidone is good

superdisintegrant as compared to cross carmellose and sodium starch glycolate. This study pondered that DT is minimum for cross povidone.

Drug release study showed that OD9 undergoes the rapid disintegration after contact with the media. Drug release profile is smoother for OD9 fig 9 as compared to all other formulations. 96% of drug is released during the 60 minute form OD9 and 97% is released from the OD1. Cross povidone showed the good release profile as compared to the other superdisintegrant.

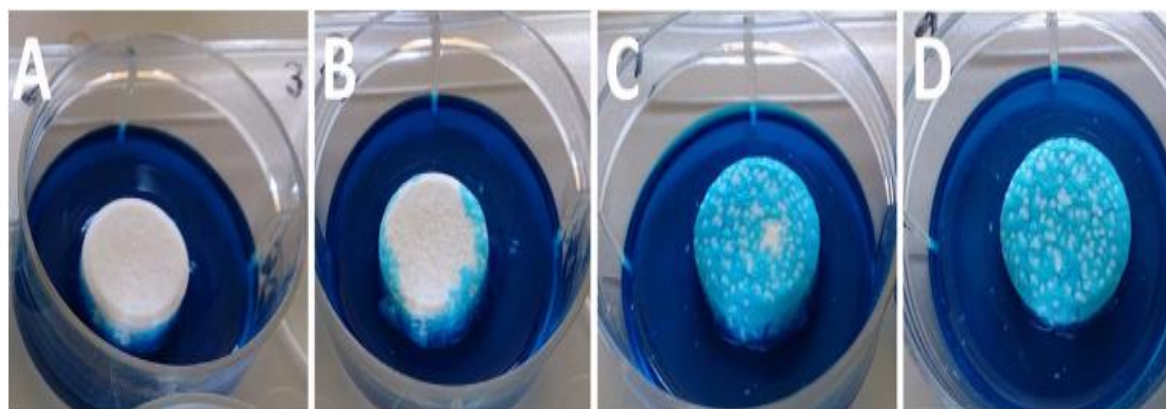


Figure 6: Wetting time of fast release tablet starting time (A) wetting of tablet (B, C) and end point (D).

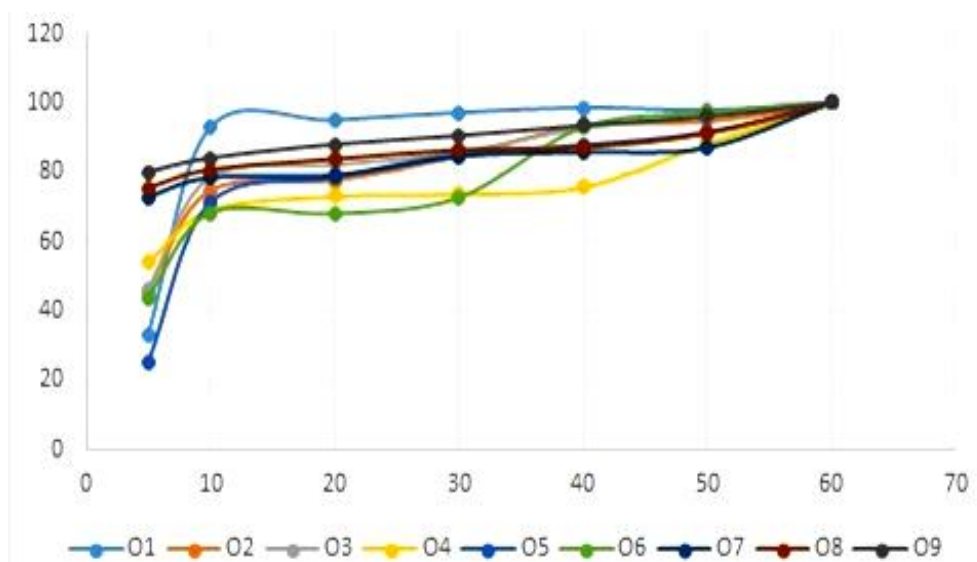


Figure 7: Dissolution profile of fast release formulations.

Table 4: Stability studies of selected directly compressed fast release tablets.

Formulation code	Time period (days)	Physical appearance	Wetting time (sec) n=5	Friability (%) n=10	Drug Assay $\pm$ S.D. n=5
OD1	15	No change in physical appearance	100 $\pm$ 0.89	0.06 $\pm$ 0.66	99.99 $\pm$ 0.03
OD2	30		50.6 $\pm$ 1.14	0.06 $\pm$ 0.65	99.97 $\pm$ 0.03
OD4	45		169.6 $\pm$ 0.55	0.19 $\pm$ 0.56	96.08 $\pm$ 0.06
OD6	60		131 $\pm$ 0.71	0.30 $\pm$ 0.51	98.06 $\pm$ 0.02
OD8	75		21.6 $\pm$ 1.34	0.19 $\pm$ 0.56	99.99 $\pm$ 0.03
OD9	90		11 $\pm$ 1.23	0.65 $\pm$ 0.66	96.02 $\pm$ 0.06

Table 5: Physical parameter to be observed in acute toxicity study for 14 days in test group.

Parameter	1hr	2hr	3hr	4hr	5hr	6hr
Weakness	×	×	×	×	×	×
Sedation	×	×	×	×	×	×
Breathing	✓	✓	✓	✓	✓	✓
Heart rate	✓	✓	✓	✓	✓	✓
Sensation	✓	✓	✓	✓	✓	✓
Activity	✓	✓	✓	✓	✓	✓
Anxiety	×	×	×	×	×	×
Tremors	×	×	×	×	×	×
Secretion (lacrima, sweating)	×	×	×	×	×	×
Excretions	×	×	×	×	×	×
Eye closure	✓	✓	✓	✓	✓	✓

Table 6: Hematology profile of controlled and test group.

Hematology	Controlled group Average $\pm$ S.D	Test group Average $\pm$ S.D
Hb	15.15 $\pm$ 0.71g/dl	15.65 $\pm$ 0.16d/dl
T L C	14.6 $\pm$ 6.35 $\times$ 10 ⁹ L	17.45 $\pm$ 3.23 $\times$ 10 ⁹ L
Total RBC	7.24 $\pm$ 0.41 $\times$ 10 ¹² L	7.51 $\pm$ 0.120 $\times$ 10 ¹² L
HCT (PCV)	50.95 $\pm$ 1.91%	52.3 $\pm$ 0.438%
M C V	70.45 $\pm$ 1.36fl	69.65 $\pm$ 0.49fl
M C H	20.9 $\pm$ 0.21pg	20.8 $\pm$ 0.109pg
M C H C	29.75 $\pm$ 0.27%	29.95 $\pm$ 0.054%
Platelets	554 $\pm$ 105.16 $\times$ 10 ⁹ L	712 $\pm$ 67.91 $\times$ 10 ⁹ L
Neutrophils	6 $\pm$ 1.09%	4.5 $\pm$ 0.54%
Lymphocytes	87.5 $\pm$ 1.64%	90 $\pm$ 1.09%
Monocytes	5 $\pm$ 1.09%	4.5 $\pm$ 0.54%
Eosinophils	1.5 $\pm$ 0.54%	1.33 $\pm$ 0.81%

Hb=Hemoglobin; RBC=Red blood cells; PCV=Packed cell volume; MCV=Mean cell volume; MCH= Mean cell hemoglobin; MCHC= Mean cell hemoglobin concentration.

Table 7: Biochemical profile of controlled and test group

Name of Tests	Controlled Group $\pm$ Average S.D*	Test group $\pm$ Average S.D*
Liver function test		
S. Bilirubin (Total)	0.308 $\pm$ 0.01mg/dl	0.355 $\pm$ 0.015mg/dl
AST	93.5 $\pm$ 29.02u/l	70 $\pm$ 47u/l
ALT	78.5 $\pm$ 24.64u/l	56 $\pm$ 42u/l
AKP	83.5 $\pm$ 27.93u/l	120.5 $\pm$ 27.5u/l
Kidney function test		
S. Proteins	6.95 $\pm$ 0.05G/dl	6.6 $\pm$ 0.2G/dl
S. Albumins	3.95 $\pm$ 0.27G/dl	4.25 $\pm$ 0.15G/dl
Blood urea	26.5 $\pm$ 7.12mg/dl	19.5 $\pm$ 3.5mg/dl
Blood urea nitrogen	12 $\pm$ 3.28mg/dl	8.5 $\pm$ 1.5mg/dl
Serum creatinine	0.745 $\pm$ 0.19mg/dl	0.635 $\pm$ 0.105mg/dl
Serum uric acid	7.2 $\pm$ 2.40mg/dl	8.55 $\pm$ 3.05mg/dl
Lipid profile		
S. Cholesterol	91 $\pm$ 3.28mg/dl	122 $\pm$ 11mg/dl
S. Triglycerides	127.5 $\pm$ 10.40mg/dl	155.5 $\pm$ 37.5mg/dl
S. High density. Cholesterol	31.5 $\pm$ 2.73mg/dl	27.5 $\pm$ 4.5mg/dl
S. Low density. Cholesterol	69.5 $\pm$ 3.834058mg/dl	88.5 $\pm$ 3.5mg/dl
VLDL Cholesterol	25 $\pm$ 2.19089mg/dl	30.5 $\pm$ 7.5mg/dl

S=serum; AST= Aspartate aminotransferase; ALT=Alanine aminotransferase; AKP= Alkaline phosphatase; S.D* =standard deviation

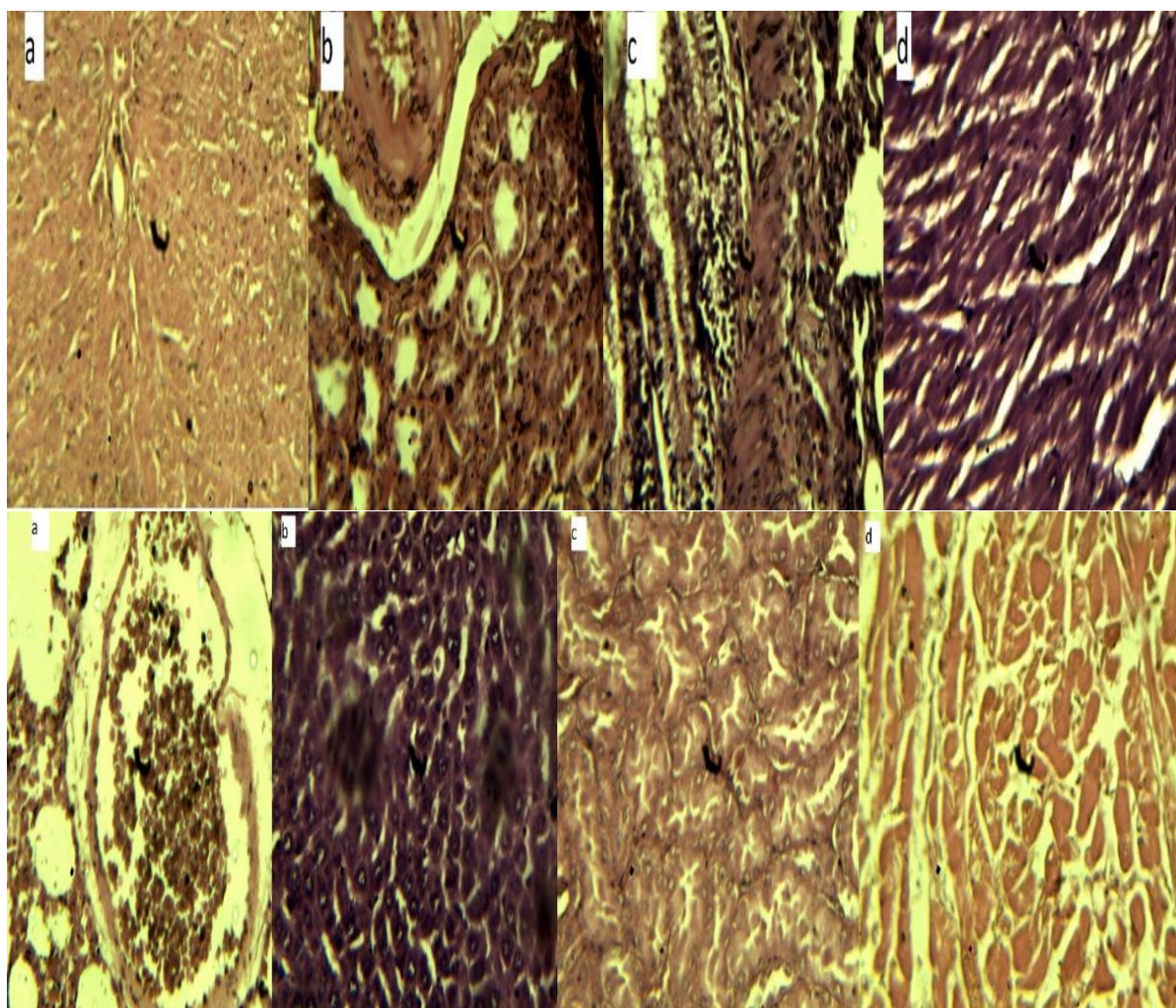


Figure 9: Controlled and test group of orodispersible tablets; Intestine (a) Liver (b) Lung (c) and Heart (d).

Stability studies (table IV) for the selected formulation did not show any changes in appearance, distortion in shape, brittleness on tablet surface. DT, friability and assay was in range of 11 ± 1.23 to 100 ± 0.89 sec, 0.06 ± 0.66 to $0.65 \pm 0.66\%$ and 96.02 ± 0.06 to $99.99\% \pm 0.03$.

Acute Toxicity Study of OD Tablets

In current study toxicity studies were conducted to check the safety profile of developed carrier dosage form. Acute toxicity studies did not result in any mortality at administered dose of developed carrier. There is no changes in physical signs (Table 5) like activity, weakness, secretion, excretion, sedation, breathing, heart rate, tremors food and water intake was observed during 14 days on regular basis. triglycerides and LDL in treatment group. These raised level are not statistically significant when compared with the results of control group. Histopathological examination (figure 8) of intestine, liver, lung and heart reveals normal histology of cell in treatment group likewise controlled group without providing the evidence of inflammation or necrosis [22].

There was no significant change observed in hematological parameters (Table 6) like Hb, TLC, R.B.C, HCT/PCV, MCV, MCH when compared with the corresponding parameters of controlled group except platelet whose count is high in treatment group which is non-significant.

Similarly, no significant changes in biochemical parameter (Table 7) like AST, ALT, AKP, bilirubin when compared to the control group. Normal values of liver function test showed that drug is nondamaging to the hepatocytes. No fatty changes and necrosis are observed in hepatocytes after giving dose. Normal Renal function showed that drug is nondamaging to renal cells. Lipid profile showed a little increase in serum cholesterol,

CONCLUSION

The results of trails batches of fast release tablets revealed that superdisintegrant controls the disintegration of particles from the formulation. Among the various superdisintegrant used; cross povidone showed the least disintegration time compared to cross carmellose and sodium starch glycolate due to wicking and swelling property as it

is porous by nature. This porosity facilitates the water and/ saliva penetration when tablet is placed inside the oral cavity leading to swelling without gel formation. Moreover, polymer concentration is rate limiting step for the DT, inverse relationship between the disintegrant concentration and disintegration time is observed. Cross povidone gives more reliable drug release profile as compared to other superdisintegrant. FTIR study showed no alteration in peaks. Acute toxicity studies showed that the directly compressed fast release tablets are safe for use.

Acknowledgement

The authors are grateful for the financial support granted by Faculty of Pharmaceutical Sciences Govt. College University Faisalabad Pakistan.

REFERENCES

1. W. D. Chey, J. Kurlander and S. Eswaran.Irritable bowel syndrome: a clinical review.Jama.2015;9 (313):949-958.
2. K. A. Gwee, U. C. Ghoshal and M. Chen.Irritable bowel syndrome in Asia: Pathogenesis, natural history, epidemiology, and management.Journal of gastroenterology and hepatology.2018;1 (33):99-110.
3. A. C. Ford, E. M. Quigley, B. E. Lacy, A. J. Lembo, Y. A. Saito, L. R. Schiller, E. E. Soffer, B. M. Spiegel and P. Moayyedi.Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: systematic review and meta-analysis.Am J Gastroenterol.2014;9 (109):1350-65; quiz 1366.
4. B. M. Spiegel.The burden of IBS: looking at metrics.Current gastroenterology reports.2009;4 (11):265-269.
5. O. Aydin and P. Ünal-Aydin.Vortioxetine treatment for major depressive disorder with the co-morbidity of irritable bowel syndrome with diarrhoea: a case report.Psychiatry and Clinical Psychopharmacology.2018;1 (28):107-109.
6. S. S. Bilge, A. Bozkurt, F. İlkaya, E. Çiftcioglu, Y. Kesim and T. I. Uzbay.The antinociceptive effects of intravenous tianeptine in colorectal distension-induced visceral pain in rats: The role of 5-HT₃ receptors.European journal of pharmacology.2012;1-3 (681):44-49.
7. M. C. Gohel, R. K. Parikh, B. K. Brahmabhatt and A. R. Shah.Preparation and assessment of novel coprocessed superdisintegrant consisting of crospovidone and sodium starch glycolate: a technical note.AAPS PharmSciTech.2007;1 (8):E63-E69.
8. D. Sharma, R. Singh and G. Singh.Orally-disintegrating Tablets in Fixed-dose Combination Containing Ambroxol Hydrochloride and Salbutamol Sulphate Prepared by Direct Compression: Formulation Design, Development and In Vitro Evaluation.Turkish Journal of Pharmaceutical Sciences.2018;1 (15).
9. M. Lal, M. Lai, M. Estrada and C. Zhu.Developing a Flexible Pediatric Dosage Form for Antiretroviral Therapy: A Fast-Dissolving Tablet.Journal of pharmaceutical sciences.2017;8 (106):2173-2177.
10. P. Mohanachandran, P. Sindhumol and T. Kiran.Superdisintegrants: an overview.International journal of pharmaceutical sciences review and research.2011;1 (6):105-109.
11. S. Yassin, D. J. Goodwin, A. Anderson, J. Sibik, D. I. Wilson, L. F. Gladden and J. A. Zeitler.The disintegration process in microcrystalline cellulose based tablets, part 1: influence of temperature, porosity and superdisintegrants.Journal of pharmaceutical sciences.2015;10 (104):3440-3450.
12. N. Abdus Salam, A. Erum, S. Bashir, M. Naeem Aamir, A. Rasul, K. Abbas, M. Riaz and A. Usman.Fabrication and Characterization of Sustained-Release Matrix Tablets: Novel Combination of Antidiabetic and Antihypertensive Drugs. Latin American Journal of Pharmacy .2018;3 (37):431-438.
13. A. Nair, D. Khunt and M. Misra.Application of quality by design for optimization of spray drying process used in drying of Risperidone nanosuspension.Powder Technology.2019 (342):156-165.
14. A. Mahmood, Ahmad, M., Sarfraz, R. M., & Minhas, M. U. β -CD based hydrogel microparticulate system to improve the solubility of acyclovir: Optimization through in-vitro, in-vivo and toxicological evaluation. Journal of Drug Delivery Science and technology.2016.
15. N. Rangu, B. C. Kumari, G. Akula and A. Jaswanth.Formulation and Evaluation of Metoprolol Orodispersible Tablets by Super Disintegration Method.Asian Journal of Pharmaceutical Research.2018;3 (8):119-124.
16. V. Dave, R. B. Yadav, R. Ahuja and S. Yadav.Formulation design and optimization of novel fast dissolving tablet of chlorpheniramine maleate by using lyophilization techniques.Bulletin of Faculty of Pharmacy, Cairo University.2017;1 (55):31-39.
17. S. A. Yehia, M. S. El-Ridi, M. I. Tadros and N. G. El-Sherif.Phenylalanine-free taste-masked orodispersible tablets of fexofenadine hydrochloride: development, in vitro evaluation and in vivo estimation of the drug pharmacokinetics in healthy human volunteers.Pharmaceutical development and technology.2015;5 (20):528-539.
18. M. Naeem, A. Mahmood, S. Khan and Z. Shahiq.Development and evaluation of controlled-

- release bilayer tablets containing microencapsulated tramadol and acetaminophen. *Tropical Journal of Pharmaceutical Research*.2010;4 (9).
19. N. Zhao and L. L. Augsburger. The influence of swelling capacity of superdisintegrants in different pH media on the dissolution of hydrochlorothiazide from directly compressed tablets. *AAPS pharmscitech*.2005;1 (6):E120-E126.
 20. V. K. Suresh, K. Ranjit, P. Nikunj, R. Someshwara, B. Ramesh and K. Aashok. Formulation and evaluation of fast disintegrating Meloxicam tablets and its comparison with marketed product. *International Journal of Pharmacy and Pharmaceutical Sciences*.2011;1 (3):134-139.
 21. M. Karthikeyan, M. A. Umarul, M. Megha and H. P. Shadeer. Formulation of diclofenac tablets for rapid pain relief. *Asian Pacific Journal of Tropical Biomedicine*.2012;1 (2):S308-S311.
 22. A. H. Yehya, M. Asif, G. Kaur, L. E. Hassan, F. S. Al-Suede, A. M. A. Majid and C. E. J. J. o. a. r. Oon. Toxicological studies of *Orthosiphon stamineus* (Misai Kucing) standardized ethanol extract in combination with gemcitabine in athymic nude mice model.2019 (15):59-68.