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Formulation and Evaluation of Floating Matrix Tablets of Tolcapone Using Psyllium Husk Powder by Non-Effervescent Method

AUTHORS

Miss. Samiksha S. Lokhande[1], Dr. Jayshree B. Taksande[2], Dr Milind D. Umekar[3].

Student, Department of Pharmaceutics, Smt. Kishoritai Bhoyar College of Pharmacy Near Dragan Palace Kamptee Nagpur.

Associate Professor, Department of Pharmaceutics, Smt. Kishoritai Bhoyar College of Pharmacy Near Dragan Palace Kamptee Nagpur

Principal, Department of Pharmaceutics, Smt. Kishoritai Bhoyar College of Pharmacy Near Dragan Palace Kamptee Nagpur

ABSTRACT

The aim of the work is to modify the bioavailability of Tolcapone, by employing non effervescent floating drug delivery (tablet dosage forms) system. Non-effervescent systems are a type of floating drug delivery systems that have been used to boost the gastric residence and the floatation time in the gastrointestinal tract. In the present study of Tolcapone floating matrix tablets were prepared by non effervescent method by using Natural Polymer (Psyllium husk) as floating agent. Psyllium husk is gastric protectant so we can overcome the gastric irritancy caused by the other added chemical excipients. The study included formulation of floating tablets using polymers like Hydroxy Propyl Methyl Cellulose (HPMC K100, & HPMC K15M), Sodium carboxy methyl Cellulose and Eudragit RS100. The tablets were prepared by direct compression technique. Fourier Transform Infra Red Spectroscopy (FTIR) and Differential Scanning Calorimetric - Thermo Gravimetric Analysis (DSC-TGA) studies confirmed that there was no incompatibility between the polymers and the drug. Tablets pre formulation parameters were within the Pharmacopoeias limit. Tablets showed zero lag time, continuance of buoyancy for
>12hrs. In- vivo X-ray studies depicted that the tablets continued to float in the Gastro Intestinal Tract for 12hrs. The in-vitro drug release pattern of Tolcapone floating tablets was fitted to different kinetic models which showed highest regression for zero order kinetics & all the formulations followed Non-fickian diffusion. Thus the prepared non-effervescent floating tablet of Tolcapone can be used for the treatment of Parkinsonism for more than 12 hrs with single dose administration.

KEY WORDS: Floating drug delivery system, Tolcapone, HPMC, Psyllium husk powder, SCMC & Eudragit RS100.

INTRODUCTION

Tolcapone is a drug used to treat Parkinson's disease (PD). It is absorbed from the upper part of gastrointestinal tract. The oral bioavailability of Tolcapone was reported to be 50%. The recommended adult oral dosage of Tolcapone is 100mg for the effective treatment of Parkinsonism. The short biological half life of drug (3 to 3.5hrs) also favors development of sustained release formulations. Drugs which are easily absorbed from the gastrointestinal tract and those with short half-lives are quickly eliminated from the systemic circulation due to which frequent dosing is required. To overcome this problem, gastro retentive drug delivery systems which provide effective plasma drug concentration for longer periods thereby reducing the dosing frequency are being formulated. It also has an advantage of minimizing the fluctuations in plasma drug concentration by delivering the drug in a controlled manner and reproducible manner.[1,2] Floating drug delivery system is also called the hydro dynamically balanced system (HBS). Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. It is applicable for those drugs which (i) act locally; (ii) have a narrow absorption window in the small intestinal region; and (iii) unstable in the intestinal environment.[3,4] The present study aims in designing floating tablets of Tolcapone using HPMC K15M, HPMC K100M, Sodium Carboxy Methyl Cellulose and Eudragit RS 100 and evaluating the prepared tablets for physicochemical properties, buoyancy lag time, total floating time, swelling index and in-vitro drug releas.

MATERIALS AND METHODS

Materials

Tolcapone was obtained as a gift sample from RA Chem Pvt.Ltd, Hyderabad and PAR Formulations, Chennai, India. HPMC K100M, HPMC K15M, SCMC, talc, magnesium stearate and lactose were received from Fourrts India Laboratories, Chennai. Eudragit RS 100 was purchased from Medrich Laboratories Pvt. Ltd Bangalore, India.

Methods

Preparation of Non-Effervescent floating matrix tablets of Tolcapone

Floating tablets of Tolcapone were prepared by direct compression method according to the formula given in Table 1A. Tocapone (100 mg) was mixed with the required quantity of polymer HPMC K100M or HPMC K15M or SCMC or Eudragit RS 100 and

Psyllium Husk, lactose in mortar and pestle for 15min. The powder blend was then lubricated with talc and magnesium stearate for additional 3min prior to the compression. The powder was then compressed into tablets.

Preparation of Effervescent floating matrix tablets of Tolcapone

Effervescent floating tablets containing Tolcapone are prepared by direct compression technique using HPMC K100M as a polymer, the formula given in Table 1B. The method was compared to the non-effervescent technique. Sodium bicarbonate used as a gas-generating agent and citric acid, lactose in mortar and pestle for 15 min.The powder blend was then lubricated with talc and magnesium stearate for additional 3min prior to the compression. The powder was then compressed into tablets.

Table 1A: Composition of different formulations of floating tablets (Non-effervescent)

F.codes	Ingredients (330mg/tablet)								
	Tolcapone	HPMC K15M	HPMC K100M	SCMC	Eudragit RS 100	PHP	Lactose	Talc	Mag. stearate
F1	100	214.5	-	-	-	3.3	6.2	4	2
F2	100	198	-	-	-	6.6	19.4	4	2
F3	100	181.5	-	-	-	9.9	32.6	4	2
F4	100	165	-	-	-	13.2	45.8	4	2
F5	100		214.5	-	-	6.6	2.9	4	2
F6	100	-	198	-	-	8.25	17.75	4	2
F7	100	-	181.5	-	-	9.9	32.6	4	2
F8	100	-	165	-	-	11.55	47.45	4	2
F9	100	-	-	115.5	-	9.9	98.6	4	2
F10	100	-	-	148.5	-	8.2	67.3	4	2
F11	100	-	-	181.5	-	6.5	36	4	2
F12	100	-	-	214.5	-	4.9	4.5	4	2
F13	100	-	-	-	115.5	16.5	92	4	2
F14	100	-	-	-	132	13.2	78.8	4	2
F15	100	-	-	-	148.5	9.9	65.6	4	2
F16	100	-	-	-	165	6.6	52.4	4	2

Table.1B Formulation of effervescent floating Tablets (F17)

Ingredients	Tolcapone	HPMC K100M	Sodium Bicarbonate	Citric Acid	Magnesium Stearate	Talc	Lactose
Quantity (mg) for 1 tablet	100	198	12	10	2	4	4

EVALUATION OF FLOATING MATRIX TABLETS

Pre compression parameters[5]

Angle of repose, Bulk density, Tapped density, Carr's compressibility index, Hausner ratio were determined to find the flow of granules during formulation.

Post compression parameters[6] Thickness and diameter

Thickness and diameter were tested in 10 different randomly selected individual tablets from each batch. The thickness and diameter of tablets were measured by digital Vernier callipers.

Hardness test

Hardness is a force required to break a tablet cross the diameter. The hardness was tested by using Monsanto hardness tester. Three tablets from each batch are used for hardness test and results are expressed in Kg/cm^2.

Weight variation test

Weight variations were tested in 20 different randomly selected individual tablets from each batch. Weight variations were measured by digital electronic balance. The averages of 20 determinations were taken and weight variation can be calculated.

Friability test

Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting free fall of tablets (6 inches) within the chamber of the friabilator. It was rotated at a rate of 25 rpm. After 100 rotations (4 min.), the tablets were taken out from the friabilator and intact tablets were again weighed collectively.

$$\text{Friability} = \frac{Weight\ loss}{Weight\ of\ tablets\ before\ operations} \times 100$$

Drug content

Ten tablets are weighed and taken in a mortar and crushed to make powder form. A quantity of powder weighing equivalent to 10mg of drug is taken in a 100ml volumetric flask and Acid buffer pH 1.2 is added. The solution is filtered using membrane filter (0.45µm) and 10 ml of filtrate is taken into 100 ml volumetric flask and made up to final volume with Acid buffer pH 1.2. Then its absorbance is measured at 270.5nm using UV Visible spectrometer. The amount of drug present in one tablet is calculated using standard graph.

Drug content = (Actual drug content / theoretical drug content) X100

In -vitro buoyancy study

The in-vitro buoyancy studies are performed for two parameters such as floating lag time (FLT) and total floating time (TFT). These parameters are determined for all the formulations of Tolcapone. The randomly selected tablets from each formulation are kept in a 100ml beaker containing acid buffer pH 1.2. The time taken for each tablets to rise on the surface and float is taken as floating lag time **(FLT).**

The total floating time of all tablets are performed by using dissolution test apparatus USP type II paddle method with a stirring speed of 50 rpm at 37°C ± 0.5°C in 900 ml of acid buffer pH 1.2 for 12 hours. The duration of time the floating tablets constantly remain on surface of medium is taken as total floating time **(TFT).**

Swelling Index Study[7]

For each formulation, one tablet is weighed and placed in a USP type II paddle dissolution test apparatus containing 900ml of acid buffer pH 1.2 with the paddle speed of 50rpm. After predetermined time the tablet is removed from apparatus, blotted to remove excess of water and weighed on digital balance. The increase in the wet mass represents the medium uptake **(swelling index).**

$$\text{Swelling Intex (\%)} = \frac{Wt - W0}{W0} \times 100$$

Where, SI is swelling index, Wt is weight of tablet at time t,
W0 is weight of tablet before immersion.

In-vitro drug release studies

Dissolution characteristics of the formulated floating tablets of Tolcapone are carried out using USP Type II (paddle) dissolution test apparatus for 12hrs.

Method

Parameter	Specifications
Dissolution Medium	Buffer 0.1N hydrochloric Acid
Temperature	37.0 ± 0.5 °C
Initial Volume	900ml
Rotation Speed	50rpm
Drawn Volume	2.5ml
Running Time	12 hrs in 0.1N hydrochloric Acid
Analyzed	270.5nm UV-Visible Spectrophotometer.

Release Kinetics Model	Equation
Zero Order	$Qt = Q_0 + K_0.t$
First Order	$In\ Qt = In\ Q_0 + K_0.t$
Hixson-Crowell	$Q_0 1/3 - Qt\ 1/3 + K.t$
Higuchi	$Q = KH.\ t1/2$
Koresmeyer - Peppas	$Mt / M_0 = a.tn$

In- vitroDRUG RELEASE KINETICS[8,9]

To analyze the in-vitro release data various kinetic models were used to describe the release kinetics. The zero order rate describes the systems where the drug release rate is independent of its concentration. The first order describes the release from the system where release rate is concentration dependent. Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on the Fickian diffusion. The Hixson-Crowell root law describes the release from the systems where there is a change in surface area and diameter of particles. The Koresmeyer-peppas describes the mode of release of drug from swellable matrices. **SIMILARITY FACTOR (f_2) ANALYSIS**

In-Vitro drug release profile of the marketed Tolcapone tablets was compared with the drug release profile of test product under similar experimental conditions. The data obtained from this drug release studies was used to determine the similarity factor between Non-effervescent and effervescent product. Similarity factors was calculated using the formula showed below.

$$f_2 = 50 \log\{[1+(1/N)\Sigma(Rt-Tt)^2]^{-0.5} x100\}$$

Where N is number of time points, Rt and Tt are dissolution of reference and test products at time **i**. If f_2 is greater than 50 then it is considered that two products have similar drug release behaviour.

RESULTS AND DISCUSSION

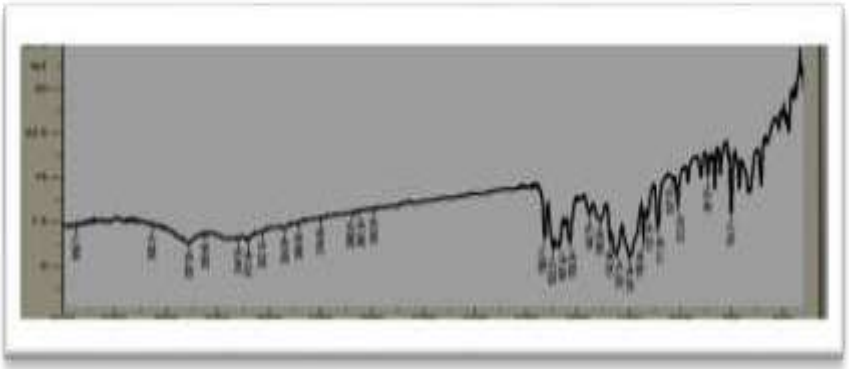
Preparation of calibration curve

Calibration curves of Tolcapone were prepared in Acid buffer pH 1.2. The absorbance was measured at λmax of 270.5nm. Tolcapone obeys beer's law within the concentration range of 2 - 20µg/ml. Calibration curve data were subjected to linear regression analysis. R^2values was found to be 0.9998 in Acid buffer pH 1.2 which indicates linearity.

DRUG-POLYMER COMPATIBILITY STUDIES

1. Fourier Transform Infrared Spectroscopic studies (FTIR)

FTIR spectra's of pure Tolcapone, blend of polymers with drug were determined. Tolcapone showed that the principle IR peaks 1324^{cm-1}, 867 $^{cm-1}$, 3387 $^{cm-1}$, 3032 $^{cm-1}$ &1660 $^{cm-1}$. All the major peaks present in the spectrum of pure drug were clearly observed in the spectrum of physical mixtures with negligible changes. The obtained results clearly showed that there was no interaction between the drug and polymers.



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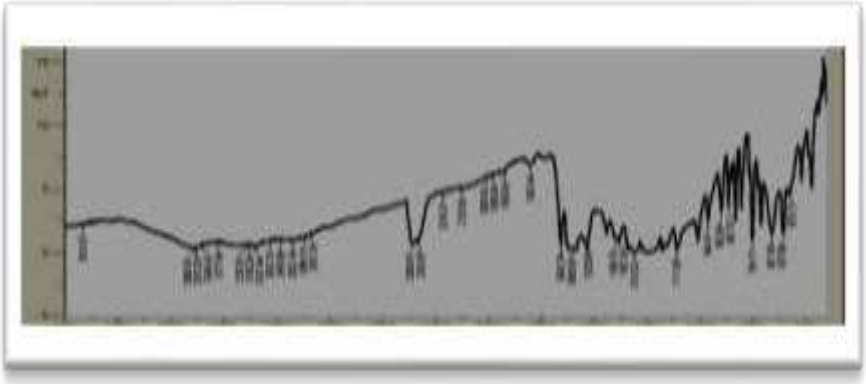

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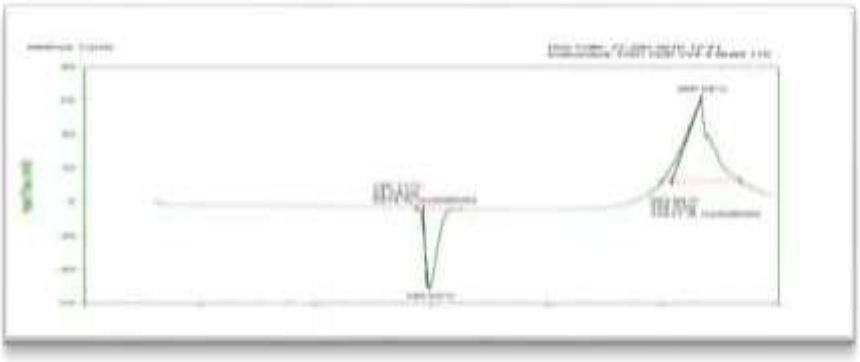
Fig 1.FTIR study

(a) Tolcapone (b) Psyllium husk powder(c) Mixture of Tolcapone+ HPMC100M+PHP

2. Differential Scanning Calorimetric (DSC) with TGA Studies

The DSC-TGA studies were carried out to detecting the drug-polymer incompatibility. Tolcapone exhibits a sharp endothermic peak at 149.03˚C.An endothermic. peak corresponding to the melting point of pure drug was prominent in all the drug polymer mixture, which suggested clearly that there was no interaction between the drug and polymer and the drug was existed in its unchanged form



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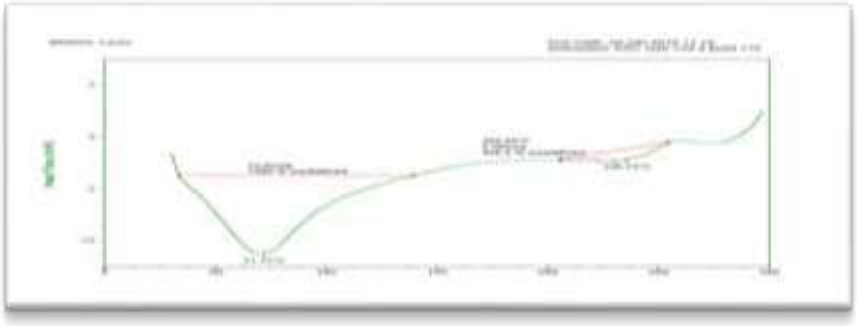

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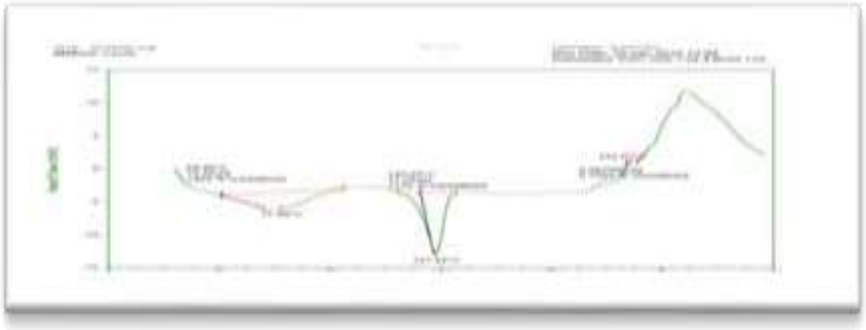


(c)

Fig 2.DSC-TGA study
(a) Tolcapone (b) Psyllium husk powder (c) Tolcapone + PHP+HPMCK100 M

PRE-COMPRESSION EVALUATIONS

Pre compression Evaluation of Powder Blend

Pre-compression parameters play an important role in improving the flow properties of pharmaceuticals especially in tablet formulation. These include bulk density, tapped density Carr's index, Hausner's ratio and Angle of repose. Before formulation of floating tablets, the drug and ingredients were evaluated for all the above said parameters and it was found that all the observations were within the prescribed limits of IP. Pre compression parameters of Tolcapone floating tablet granules are shown in Table 2. The bulk density of the formulation ranged between 0.523 ± 0.03g/mL and 0.583 ± 0.18g/mL. Tapped density varied between 0.531 ± 0.02g/mL and 0.603 ± 0.01g/mL. Carr's index value ranged between 7.70 ± 1.90 to 10.82 ± 1.58. Hausner's ratio was found between 1.01 ± 0.01 to 1.12 ± 0.02, Angle of repose has been used as indirect method of quantifying power flow ability, and fallen between 21º20' ± 1.23 to 28º58' ± 1.66 and drug content of all formulations between 98.45 ± 1.21 to 101.94 ± 1.50. All the formulations were fallen in good flow character based on angle of repose, compressibility index and Hausner ratio reports. The pre compression evaluation for all formulations showed in table 2.

Table: 2 Pre compression Evaluation of Powder Blend

F.code	Angle of repose (θ) ±SD	Bulk density (gm/ml)±SD	Tapped density (gm/ml) ±SD	Carr,s index (%) ±SD	Hausners Ratio ±SD	Drug content ± SD
F1	23º10' ± 2.31	0.563 ± 0.018	0.566 ± 0.022	8.227 ± 0.69	1.01 ± 0.01	99.78±0.53
F2	25º62' ± 1.67	0.534 ± 0.032	0.603 ± 0.013	7.443 ± 0.035	1.10 ± 0.01	98.53±0.58
F3	25^{0}42' ± 2.21	0.527 ± 0.012	0.592 ± 0.040	9.987 ± 0.472	1.11± 0.02	101.2±0.81
F4	25^{0}76' ± 0.78	0.554 ± 0.054	0.589 ± 0.025	8.620 ± 1.283	1.06 ± 0.01	100.99±0.49

F5	$27^0$86'± 2.11	0.561 ± 0.049	0.570 ± 0.006	8.310 ± 1.100	1.00 ± 0.01	101.94±1.5
F6	$27^0$62'± 0.78	0.547 ± 0.034	0.553 ± 0.012	8.323 ± 1.450	1.01 ± 0.01	99.82±0.77
F7	$25^0$09' ±101	0.523 ± 0.039	0.531 ± 0.028	7.717 ± 0.138	1.02 ± 0.02	99.76±1.48
F8	$25^0$85' ± 1.53	0.528 ±0.008	0.535 ± 0.012	10.820 ± 1.58	1.03 ±0.03	99.82±0.77
F9	$26^0$48' ± 1.48	0.583 ± 0.018	0.545 ± 0.018	8.553 ± 1.085	1.06 ± 0.03	99.89±0.99
F10	$22^0$92' ± 0.72	0.525 ± 0.045	0.568 ± 0.013	7.330 ±2.503	1.02 ± 0.03	98.45±1.21
F11	$27^0$88' ± 2.03	0.536 ±0.031	0.553 ± 0.014	7.700 ± 1.901	1.03 ± 0.04	98.67 ± 0.89
F12	$21^0$20'± 1.23	0.543 ±0.043	0.545 ± 0.019	8.490 ± 1.923	1.01 ± 0.02	99.60 ± 0.10
F13	$28^0$58' ± 1.66	0.538 ± 0.012	0.544 ± 0.020	7.967 ± 1.408	1.02 ± 0.03	100.19 ± 0.19
F14	$24^0$93' ± 2.33	0.531 ± 0.031	0.573 ± 0.042	9.410 ± 0.570	1.06 ± 0.03	98.71±1.32
F15	$23^0$87'±1.53	0.534 ± 0.021	0.559 ± 0.022	8.137 ± 1.515	1.12 ± 0.02	99.79±0.99
F16	$27^0$59' ± 0.72	0.530 ± 0.021	0.598 ± 0.020	8.440 ± 0.589	1.12 ± 0.02	100.71±1.43
F17	$23^0$09' ± 1.12	0.553 ± 0.015	0.587 ± 0.014	7.463 ± 1.933	1.077 ± 0.021	99.52±1.53

POST-COMPRESSION EVALUATIONS

Post compression evaluation of floating matrix tablets Post-compression parameters of Tolcapone floating matrix tablets are showed in Table 3. The tablets prepared from all formulations were evaluated for quality control parameters, Weight variation, Hardness, thickness, Friability, and Drug content uniformity. All formulations had average tablet weight in the range of 320.01±0.94mg to 324.65±1.96mg. Thickness ranged between 3.83±0.05mm and 3.96±0.05mm. The hardness lies between 2.66±0.28Kg/cm^2 and 3.83±0.27Kg/cm^2. The friability of all floating matrix tablets of Tolcapone was found between 0.37% and 0.80%. Drug content ranged between 96.90±0.19% to 100.45±0.30%.The thickness of the floating tablet indicated that die fill was uniform. The thickness depends upon the size of the punch (9.5 mm) and the weight of the tablet (330 mg). Friability is needed for tablets to withstand force of compression applied during the manufacture of tablets and all the formulated floating tablets of Tolcapone were shown the percentage friability within the official limits (i.e. not more than 1%). Formulations showed favourable drug content which were within the limits of specifications.

Table 3.Post Compression Evaluation of Tolcapone Floating Matrix Tablets

F. code	Hardness (kg/cm²) ±SD	Diameter (mm)	Thickness (mm) ±SD	Friability (%) ±SD	Average weight(mg) ±SD	Drug content(%) ±SD
F1	3.16 ± 0.28	9.5	3.86 ± 0.057	0.55 ± 0.19	320.86 ± 1.52	96.90 ± 0.19
F2	2.83 ± 0.28	9.5	3.86 ± 0.057	0.44 ± 0.19	320.01 ± 0.94	98.32 ± 0.29
F3	3.16 ± 0.28	9.5	3.86 ± 0.057	0.55 ± 0.19	322.6 ± 1.10	98.77 ± 0.11
F4	2.66 ± 0.28	9.5	3.86 ± 0.057	0.55 ± 0.22	321.04 ± 0.88	99.61 ± 0.69
F5	3.16 ± 0.57	9.5	3.93 ± 0.057	0.68 ± 0.34	321.92 ± 1.04	100.19 ± 0.19
F6	3.16 ± 0.57	9.5	3.86 ± 0.057	0.79 ± 0.19	321.40 ± 1.58	99.67 ± 0.10
F7	3.16 ± 0.28	9.5	3.93 ± 0.057	0.45 ± 0.19	322.21 ± 1.58	99.60 ± 0.10
F8	3.16 ± 0.28	9.5	3.96 ± 0.057	0.79 ± 0.19	321.1 ± 1.57	98.67 ± 0.89
F9	3.16 ± 0.28	9.5	3.86 ± 0.057	0.55 ± 0.27	320.71 ± 1.25	98.67 ± 0.89
F10	3.66 ± 0.28	9.5	3.96 ± 0.057	0.55 ± 0.19	320.37 ± 1.57	99.99 ± 0.19
F11	3.83 ± 0.27	9.5	3.96 ± 0.057	0.44 ± 0.19	323.66 ± 1.95	100.88 ± 0.50
F12	3.66 ± 0.57	9.5	3.83 ± 0.057	0.55 ± 0.19	322.73 ± 0.95	100.38 ± 0.50
F13	3.66 ± 0.57	9.5	3.96 ± 0.057	0.68 ± 0.34	324.65 ± 1.96	99.73 ± 0.95
F14	3.83 ± 0.28	9.5	3.86 ± 0.057	0.58 ± 0.19	320.2 ± 0.52	99.03 ± 0.19
F15	3.16 ± 0.28	9.5	3.86 ± 0.057	0.90 ± 0.19	320.66 ± 1.61	99.86 ± 0.73
F16	3.83 ± 0.28	9.5	3.83 ± 0.057	0.68 ± 0.39	323.03 ± 1.09	100.45 ± 0.30
F17	3.53 ± 0.06	9.5	3.90 ± 0.10	0.58 ± 0.20	323.49±1.81	95.21 ± 0.56

In-vitro buoyancy & swelling test

The in-vitro buoyancy properties namely floating lag time, total floating time and swelling characters of prepared floating matrix tablets based on the polymer concentration and density. The formulations F1 to F8 comprises of higher polymer concentration and low density of HPMC K15 and HPMC K100 in various proportions which makes them floats immediately compared to other formulations (F9-F17) containing SCMC and Eudragit RS100, Except F12 (Higher polymer concentration). The Psyllium husk (1-4%) powder enhanced the floating duration and maintained the dimensional stability of all formulations. In addition the formulations F1-F8 buoyancy properties were enhanced by Psyllium husk powder (PHP) because of minimal density and maximum polymer concentration. The drug release was sustained properly up to 12 hrs. The in-vitro floating behavior of all formulations showed below.

Table: 4. In-vitro Floating Ability of Floating Matrix Tablets

Formulation Code	Buoyancy lag time (in minutes)	Total floating time(in hrs)	Swelling index (%)
F1	Immediately	>12	200.49
F2	Immediately	>12	209.60

F3	Immediately	>12	211.32
F4	Immediately	>12	231.01
F5	Immediately	10	185.98
F6	Immediately	>12	201.79
F7	Immediately	>12	250.54
F8	Immediately	>12	241.51
F9	15	10	184.50
F10	10	10	206.04
F11	10	10	210.54
F12	Immediately	11	213.04
F13	10	8	181.98
F14	10	9	194.47
F15	7	9	195.00
F16	5	>12	210.63
F17	10sec	>12	235.10

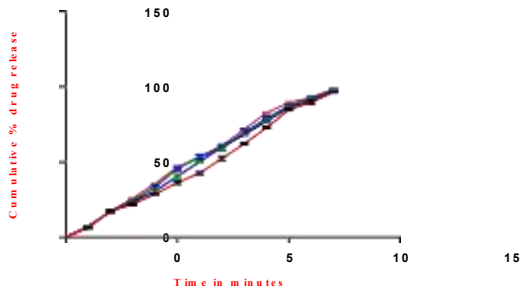
FLT (Immediately) **After 12hrs**

Fig: 3 In-vitro buoyancy and swelling behaviour of best formulation F7

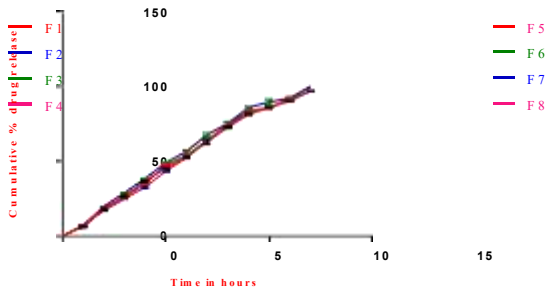
In -vitro drug release

In-vitro dissolution studies of all the formulations of floating tablets of Tolcapone were carried out in Acid buffer (0.1 N HCl). The study was performed for 12 hrs, and cumulative drug release was calculated at different time intervals.

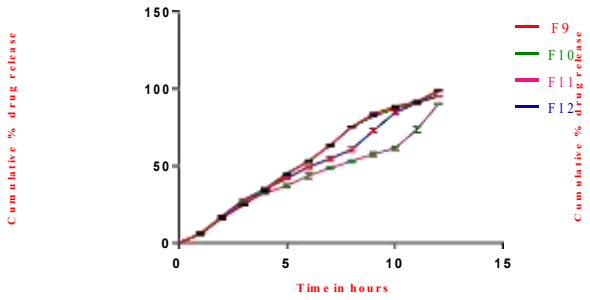
In-vitro drug release studies of formulations containing HPMC K15M (F1-F4) (65%, 60%, 55%, & 50%) showed the drug release of 96.49 %, 97.39%, 98.07 % & 98.36 at the end of 12hrs respectively. In-vitro drug release studies of formulations containing HPMC K100M (F5-F8) (65%, 60%, 55%, & 50%) showed the drug release of 96.97 %, 97.14 %, 99.75 %, & 99.98% at the end of 12hrs respectively. In vitro drug release studies of formulations containing SCMC (F9-F12) (35%, 45%, 55%, & 65%) showed the drug release of 99.03 %, 98.03 %, 88.35 %, & 95.26 % at the end of 12hrs respectively. In vitro drug release studies of formulations containing Eudragit RS100 (F13-F16) (35%, 40%, 45%, & 50%) showed the drug release of 96.08 %, 95.62 %, 94.48, & 93.52% at end of 12hrs respectively. Controlled release profiles were observed in the following order, HPMC K100M > HPMC K15M > Eudragit RS100> SCMC irrespective of the type of polymer. This may be due to the increasing tortuosity and diffusional path length through the matrix as the polymer content increases.



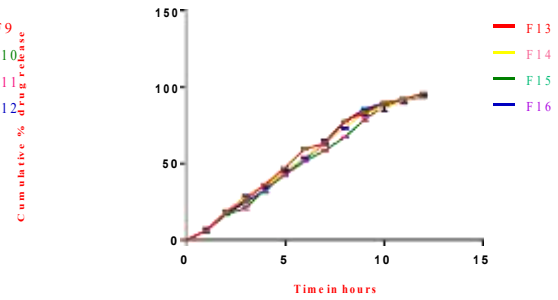
Tolcapone with HPMC K15M



Tolcapone with HPMC K100M



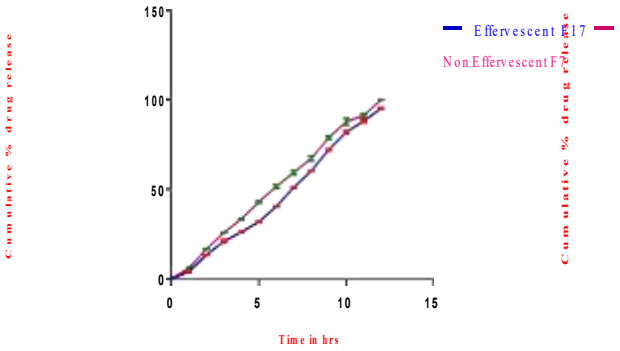
Tolcapone with SCMC



Tolcapone with Eudragitrs100 Fig: 4 In-vitro drug release profile

Among all the formulations, F7 (HPMC K100M-55%) had the best formulation on the basis of in-vitro drug release, floating lag time, total floating time and swelling index. It showed maximum drug release in a controlled manner (99.75% in 12hrs) because the formation of strong viscous gel layer that slowed down the rate of diffusion of medium into the tablet.

The in-vitro dug release of F7 best formulation (non-effervescent technique) was compared to the effervescent technique (F17) & marketed product and it shows the drug release 95.21% & 102.28%.



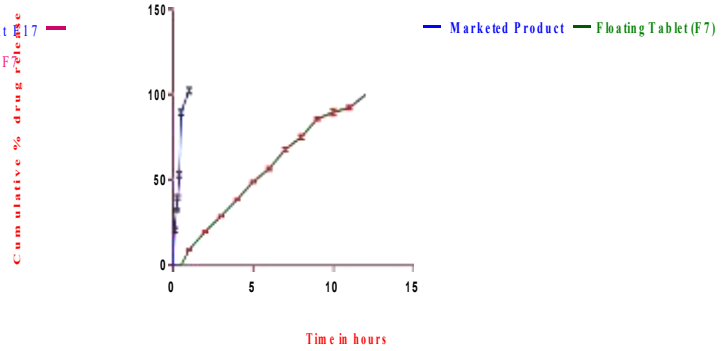


Fig.5 Comparision of Best formulation (F7) with Effervescent Tablet (F17) & Marketed Tablets

SIMILARITY FACTOR (f_2) ANALYSIS

The similarity factor f_2 is the simple measure for the comparison of two dissolution profile. It ensures the uniformity of product from batch to batch and help to predict bioavailability for formulation development. The similarity factor analysis between prepared non- effervescent tablets and effervescent tablets showed the f_2 factor (f_2=53.84) greater than 50. The f_2 factors confirm that the formulated preparation F7 shows similar drug release compare to effervescent preparation. The results are summarized below table 5.

Table: 5 Similarity factors (f2) of Floating Matrix Tablets

Time in Hrs	R_t	T_t	$R_t - T_t$	$(Rt-Rt)^2$	Number of points
1	9.06	4.02	5.04	25.40	
2	19.72	13.38	6.34	40.20	12
3	28.76	20.98	7.78	60.53	
4	38.47	26.23	12.24	149.82	
5	48.92	31.8	17.12	293.09	
6	56.55	40.39	16.16	261.15	
7	67.72	51.09	16.63	276.56	
8	75.17	60.25	14.92	222.61	
9	85.77	72.05	13.72	188.24	
10	89.65	81.89	7.76	60.22	
11	92.19	88.12	4.07	16.56	
12	99.75	95.21	4.54	20.61	
			f	64.68	
			g	830.18	
			d	201.48	
			Similarity(f2)	53.84	

			difference(f1)	32.10

RELEASE KINETICS

The release data (1-12hrs) were analyzed as per zero order, first order, Hixson Crowell, Higuchi and Korsemeyer-Peppas equation. The r2value of best formulation for zero order and first order equation was found 0.997 and 0.938 respectively. It shows that the formulation follow Zero order release. To confirm the exact mechanism of drug release from the tablets, the data were subjected to Hixson Crowell, Korsemeyer- Peppas equation and Higuchi's diffusion equation. The R^2- values for Hixson Crowell, Korsemeyer-Peppas equation and Higuchi's diffusion equation for the best formulation was found as 0.979, 0.996 and 0.938 respectively. It shows that the best fit model for the formulation is Korsemeyers-peppas model.

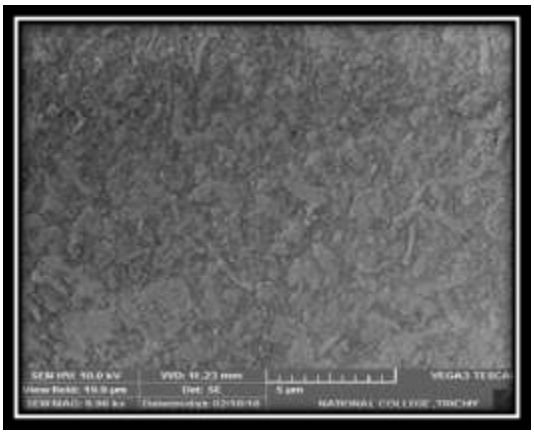
Table: 6 In-vitro Release Kinetics Data of Tolcapone Floating Matrix Tablets

F.Code	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Koresmeyer-Peppas		Hixson crowell (R^2)	Release Mechanism
				R^2	n		
F1	0.993	0.836	0.894	0.993	0.840	0.923	Non-fickian
F2	0.995	0.836	0.917	0.995	0.862	0.953	Non-fickian
F3	0.996	0.829	0.927	0.990	0.853	0.939	Non-fickian
F4	0.990	0.917	0.931	0.984	0.834	0.973	Non-fickian
F5	0.988	0.911	0.926	0.985	0.876	0.954	Non-fickian
F6	0.989	0.906	0.935	0.987	0.888	0.958	Non-fickian
F7	0.997	0.938	0.938	0.996	0.827	0.979	Non-fickian
F8	0.987	0.909	0.920	0.984	0.843	0.947	Non-fickian
F9	0.990	0.824	0.926	0.992	0.857	0.952	Non-fickian
F10	0.991	0.811	0.929	0.989	0.838	0.943	Non-fickian
F11	0.978	0.827	0.827	0.969	0.856	0.869	Non-fickian
F12	0.994	0.867	0.924	0.982	0.863	0.938	Non-fickian
F13	0.985	0.933	0.936	0.985	0.852	0.968	Non-fickian
F14	0.985	0.934	0.927	0.985	0.847	0.977	Non-fickian
F15	0.989	0.922	0.931	0.987	0.868	0.978	Non-fickian
F16	0.990	0.928	0.935	0.988	0.881	0.961	Non-fickian

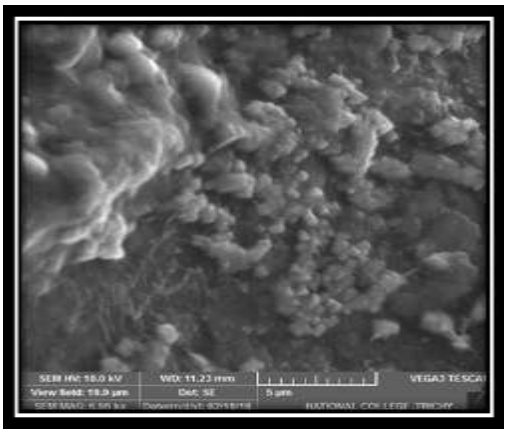
Slope value (n) in Korsemeyer-Peppas equation for formulation was found as 0.827 which is greater than 0.5 (n= >0.5) suggested that the release of Tolcapone floating tablets followed the Non-Fickian transport mechanism.

Scanning Electron Microscopy (SEM)

The surface topography, texture and morphology of fractured surface of best formulation were evaluated by using SEM. The SEM images of the tablets were taken before and after dissolution. The SEM images of the tablet showed intact surface without any perforations, channels or troughs. After dissolution the solvent front enters the matrix and moves slowly toward centre of the tablet. The drug diffuses out of the matrix after it comes in contact with dissolution medium. The SEM images of the formulation showed a network in the swollen polymer through which the drug diffused to the surrounding medium. Hence it was concluded that the drug was release from the matrix the diffusion mechanism.



Before Dissolution formulation (F7)



After Dissolution Fig.6 SEM of best

In-vivo x-ray studies

F7 containing HPMC K100M polymer have shown best and satisfactory results. Hence, this formulation was selected for further in-vivo evaluations. The in-vivo x- ray studies were carried out after getting clearance from Institutional Animal Ethical Committee (IAEC/KMCP/215). The in-vivo radiographic studies were performed in health male albino rabbits at periodic time intervals (0, 2, 4, 6, 8, 10 and 12hrs) using x-ray machine.

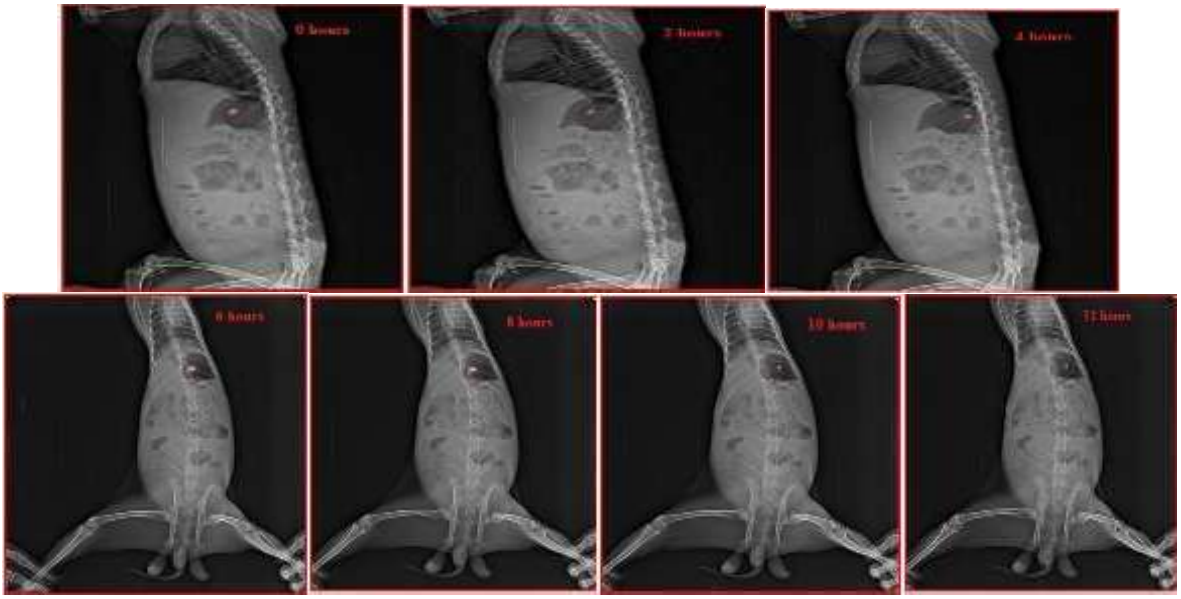


Fig.7 In-vivo X-ray study of best formulation (F7)

CONCLUSION

The results conclusively demonstrated that floating tablets of Tolcapone were effectively prepared by direct compression method with desired properties and exhibited better in-vitro drug release profiles. The formulation F7 containing HPMC K100M and Psyllium husk exhibit least floating lag time and maximum rate of drug release (>12h). So, this formulation was considered to be the optimized formulation. All of the formulations exhibited Non-fickian diffusion. Thus the formulated floating tablets of Tolcapone offer a superior alternative to improve the patient compliance over other dosage forms. Use of Hydrophilic polymers with Psyllium husk powder enhanced the floating duration and maintained the dimensional stability, which is an important requirement. The drug release was sustained properly upto 12 hrs. Based on this work it was found that non- effervescent type of floating drug delivery systems holds a lot of potential and comparable with effervescent systems & marketed formulations.

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