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Original Research Article

FORMULATION AND EVALUATION OF EXTENDED RELEASE TABLETS OF PALIPERIDONE

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ABSTRACT

The present research work was an attempt to formulate and Evaluate paliperidone extended release tablets. A combination of Hydroxy propyl methyl cellulose (HPMC K100M) and PVP, poly ethylene oxide were used as polymers. The tablets were prepared by direct compression method 12 formulations were prepared by changing the ratios of the drug and polymer to study the effect of variable concentrations of polymers and characteristics of the tablets. The prepared tablets were evaluated by different parameters such as Thickness, Weight variation, Hardness, Content Uniformity. The tablets were also evaluated for in vitro drug release in 0.1N HCl for 12 h in USP Type II dissolution apparatus. Among all the formulations (F-I to F-XII) prepared, batch F-12 gave relatively slow release of Paliperidone over 24 h when compared to other formulations. The invitro data is fitted in to different kinetic models and the best-fit was achieved with the Korsmeyer-Peppas model. Hence, formulation F12 was found to be equivalent to marketed product with good bioavailability properties. It also showed no significant change in physical appearance, Drug content. The drug carrier interactions were investigated in the solid state by Fourier transform infrared spectroscopic study(FTIR), which was further confirmed by DSC.

Key words: Paliperidone, HPMC, PVP, Poly ethylene oxide, Evaluation parameters, In-vitro dissolution studies, release kinetics.

INTRODUCTION

Extended release drug delivery systems are designed to release drug in a pre-determined manner over an extended period of time. An extended - release dosage form maybe desirable to provide patients with a convenient dosage regimen that allows less frequent dosing thus enhancing compliance. Extended release dosing can reduce peak-related side effects maintain therapeutic concentrations throughout the dosing period avoiding periods of insufficient therapeutic plasma concentrations between doses and enable a less frequent dosing regimen. Extended drug delivery systems are beneficial especially for the patients who are not able to take the medicine frequently specially in geriatric and mental patients.

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms .The reasons that the oral route achieved such popularity may be in part of its ease of administration as well as the traditional belief that by oral administration. The drug is well absorbed as the food stuffs that are ingested daily. The development of a pharmaceutical product for oral delivery irrespective of its physical forms (solid, semisolid, or oral liquid dosage form) involves varying extents of optimization of dosage form characteristics within the inherent constraints of gastrointestinal physiology.

Oral dosage forms are taken orally for a local effect in the mouth, throat or gastrointestinal tract or for a systemic effect in the body after absorption from the mouth or gastrointestinal tract. Oral dosage forms can be divided into two main groups based on the physical state of the dosage form, solid oral dosage forms (tablets, capsules or powders)and liquid oral dosage forms(solutions, syrups, emulsions, and powders for suspensions).

Paliperidone is the major active metabolite of Risperidone. It is a second-generation antipsychotic that has been developed as an extended-release (ER) tablet formulation that minimizes peak-trough fluctuations in plasma concentrations, allowing once-daily administration and constant drug delivery. Paliperidone ER was associated with a more rapid symptom improvement. In addition, it was more effective than placebo in the prevention of symptom recurrence. Paliperidone ER is generally well tolerated with a predictable adverse event profile. Like Risperidone, it is associated with a dose-dependent risk of extrapyramidal symptoms and prolactin elevation. Short- and longer-term studies have indicated a low liability for Paliperidone ER to cause metabolic (ie, weight gain, hyperglycemia and lipid

deregulation) or cardiovascular adverse effects. Available safety data from elderly patients appear to be promising. Due to negligible hepatic biotransformation, Paliperidone ER is unlikely to be involved in clinically significant metabolic drug-drug interactions. Additional active comparator trials evaluating efficacy, tolerability and cost-effectiveness are required to better define the role of Paliperidone ER in the treatment of schizophrenia in relation to other currently available second-generation antipsychotics, particularly Risperidone.

Paliperidone (trade name Invega), also known as 9-hydroxyrisperidone, is a dopamine antagonist of the atypical antipsychotic class of medications. It is developed by Janssen Pharmaceutica. Invega is an extended release formulation of paliperidone that uses the OROS extended release system to allow for once-daily dosing. Paliperidonepalmitate (trade name Invega Sustenna, named Xeplion in Europe) is a long-acting injectable formulation of paliperidone palmitoyl ester indicated for once-monthly injection after an initial titration period. Paliperidone is used to treat mania and at lower doses as maintenance for bipolar disorder. It is also used for schizophrenia and schizoaffective disorder.

Paliperidone is the primary active metabolite of the older antipsychotic risperidone. Paliperidone has antagonist effect at α1 and α2 adrenergic receptors and at H1 histamine receptors. It does not bind to muscarinic acetylcholine receptors. In addition it binds with dopamine and serotonin receptors.

Paliperidone (as Invega) was approved by the FDA for the treatment of schizophrenia in 2006. It is marketed for the treatment of schizophrenia and schizoaffective disorder. Paliperidone was approved by the FDA for the treatment of schizoaffective disorder in 2009. It may also be used off-label for other conditions. Recently, the long-acting injectable form of paliperidone, marketed as INVEGA Sustenna in U.S. and Xeplion in Europe, was approved by the FDA on July 31, 2009. It was approved in Europe in 2011 for schizophrenia. In Europe the monthly (every 28 days) injection comes in 50 mg, 75 mg, 100 mg, and 150 mg of paliperidone without the 25 mg injection that is available in the U.S. A dose of 75 mg for a month in an injection is the equivalent of 6 mg per day of paliperidone oral. 6 mg of paliperidone oral (Invega) is equivalent to 2 to 3 mg of risperidone.

MATERIALS AND METHOD

MATERIALS:

Paliperidone was obtained as a gift sample from active pharma labs ltd. HPMC, PEO, PVP, Microcrystalline Cellulose, Magnesium Stearate, Stearic Acid, were obtained from SD Chemicals Mumbai. All the ingredients used were of analytical grade.

METHOD

Preparation of Paliperidone Extended release Tablets

Trials were planned to study the effect of various polymers at different concentrations on drug release Kinetics. The direct compression was selected as process of preparation of Paliperidone tablets. The HPMC, PEO, PVP were used as release controlling polymer in various concentrations. Micro-crystalline cellulose was used as diluent. The Magnesium Stearate, Stearicacid were used as Lubricant respectively.

The various steps involved are:

1. Screening

Weigh all ingredients except the lubricant and screen them (60 mesh screen). Add the low density material first and the high density material at the end. It is beneficial to combine materials with poor flowability, small particle size or static charge with another material in order to improve the overall handling of the powder blend.

2. Mixing

Mix the powder blend to achieve content uniformity. Add the lubricant to the powder blend and mix for 2 - 5 minutes (avoid over mixing and over lubrication).

EVALUATIONPARAMETERS:

Precompression parameters

Flow properties of Paliperidone: The flow properties of the drug molecules are the important factor in selection of manufacturing process of formulation. The Hausner's ratio and compressibility index were calculated from the values of densities.

Limits for blend characterization

Compressibility index	Hausner's ratio	Flow Character
<10	1.00-1.11	Excellent
11-15	1.12-1.18	Good
16-20	1.19-1.25	Fair
21-25	1.26-1.34	Passable
26-31	1.35-1.45	Poor
32-37	1.46-1.56	Very poor
>38	>1.60	Very Very Poor

Angle of repose:

A funnel was kept vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom is closed and 10 gm of powder is filled in funnel. Then funnel was opened to release the powder on the paper to form a smooth conical heap, is found by measuring in different direction. The height of the heap was measured by using scale. The value of angle of repose is calculated by using the following formula:

$$\mathbf{Tan\ \theta = h/r}$$

$$\mathbf{\theta = Tan^{-1}\ (h/r)}$$

Where, h- height of the heap

r- Radius of the heap

Flow Properties Based on Angle of Repose

Angle of repose (in degrees)	Type of flow
<25	Excellent
25-30	Good
30-40	Pass to fail
>40	Very poor

Bulk density

- Around 10g (M) of sample was weighed and transferred to a 50ml measuring cylinder.
- The volume (V0) was noted.
- B.D was calculated using the following formula ; **B.D = M / V0**

Tapped density

- The measuring cylinder of the previous test was mounted on the Tapped density apparatus (USP I)
- Tapped 500 times and volume was noted as Va.
- Tapped 750 times and volume was noted as Vb. (if the difference between Va and Vb was more than 0.2% then tapped for more 1250 times)
- The final volume was noted as Vf.
- T.D was calculated using the following formula – **T.D = M / Vf**

Hausner's ratio (H.R)

- Hausner's ratio was calculated using the following formula; **H.R = T.D / B.D**

Compressibility index (C.I)

- Compressibility index was calculated using the following formula:

  C.I = 100 X (1 – 1/H.R.)

Estimation of drug content: Five tablets were powdered. The powdered sample equivalent to 450 mg of drug was transferred to a 100ml volumetric flask, volume was made up to 100ml with 0.1N HCl, sonicate for 60 minutes and filter the solution. From the filtrate, 1ml was

transferred to 100ml volumetric flask and the volume was made up to 100ml with 0.1N HCl. The sample was analyzed against blank by UV-Visible spectrophotometer at 237 nm.

Assay = Drug content (practically/ Drug content (Theoretically) × 100

Dissolution studies:

The tablets were further evaluated for the dissolution studies in media as given below:

1) Medium : 0.1N HCL
2) Volume : 900ml
3) Apparatus : USP-II (Paddle)
4) Rpm : 100
5) Temperature : 37±0.5°c
6) Time points : For every 1hr up to 24 hrs

Dissolution Procedure: 900 ml of 0.1N HCl was taken in a USP-II (Paddle) type apparatus at given temperature and dissolution was carried out for 24hrs at 100 rpm. The samples were withdrawn at particular interval and analyzed by UV-Visible spectrophotometer at 237 nm.

RESULTS

Pre-formulation Studies

FTIR spectral analysis was carried out to rule out the possibility of drug-excipient interaction.Vibrational spectroscopy (IR) describes same kind of molecular information and can be used to supplement or complement each other. Middle IR (400–4000cm–1; vibration-rotation region) was used for analytical purpose. The atoms held by a chemical bonds are the main participants in vibration. Vibrations depend on mass of two vibrating atoms, force constant of bond between two atoms and other atoms attached. Thus vibrations are characteristic for a group. In FTIR spectrogram results, the functional region is important for stretching and the fingerprint region for bending. Transmission peaks at 3000–3100 cm–1 indicated aromatic functional group and 3300–3700 cm–1 indicated hydrogen bonding (O-H).

Table.1.Composition of Various Formulations by direct compression method

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Paliperidone	3	3	3	3	3	3	3	3	3	3	3	3
HPMC	30	30	30	35	35	35	40	40	40	25	25	30
PEO	30	35	40	30	35	40	30	35	40	20	25	25
MCC	31.4	26.4	21.4	26.4	22.4	16.4	21.4	16.4	11.4	46	41.04	36.04
PVP	5	5	5	5	5	5	5	5	5	5	5	5
Stearic acid	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Weight(mg)	100	100	100	100	100	100	100	100	100	100	100	100

Table.2.Pre compression parameters of the various batches of the Paliperidone tablet blend

Formulation code	Bulk Density	Tapped Density	Angle of Repose	Carr's Index	Haussner's Ratio
F1	0.426±0.003	0.485±0.35	27.23±0.52	12.1±0.6	1.14±0.09
F2	0.412±0.008	0.467±0.83	26.45±0.21	11.7±0.5	1.13±0.04
F3	0.436±0.005	0.502±0.10	23.56±0.26	13.1±0.4	1.15±0.05
F4	0.443±0.009	0.509±0.21	28.97±0.21	12.9±0.7	1.15±0.09
F5	0.472±0.003	0.539±0.19	21.74±0.09	12.4±0.7	1.14±0.08
F6	0.423±0.009	0.478±0.16	25.43±0.08	11.5±0.6	1.13±0.09
F7	0.423±0.009	0.478±0.78	23.26±0.17	11.5±0.7	1.13±0.07
F8	0.418±0.006	0.473±0.41	24.12±0.23	12.0±0.5	1.13±0.06
F9	0.453±0.003	0.517±0.45	28.20±0.45	12.3±0.5	1.14±0.03
F10	0.457±0.006	0.512±0.81	29.04±0.09	11.5±0.7	1.12±0.09
F11	0.482±0.005	0.553±0.42	26.86±0.08	12.8±0.6	1.14±0.07
F12	0.424±0.008	0.475±0.84	27.61±0.13	10.9±0.4	1.12±0.08

Angle of repose: The angle of repose of all the developed formulations F1 to F12 was found to be 21.74±0.09 to 29.04 ±0.09 C as indicated in Table. According to USP – if the angle of repose is 25 -35, it shows good flow property. So the present granules are within the limits.

Bulk and tapped densities: The bulk density of the formulations F1 to F12was found to vary between 0.412± 0.008to 0.482 ± 0.005 gm/ml as indicated in the table. Tapped density was found to be 0.467± 0.83 to 0.553 ± 0.42gm/ml for formulations F1 to F12 as indicated in the table. Both are having low standard deviations.

Carr's Compressibility Index: The Carr's index was found to be10.09 ± 0.4 to 13.01 ± 0.4% for formulations F1 to F12 as indicated in the table. These values were found to be within pharmacopeial limits and having good to possible flow properties. The standard deviation was also very low.

Hausner's ratio: Hausner's ratio was found to be 1.12 ± 0.08 to1.15 ± 0.05 for the formulations F1 to F12 as indicated in the table. These values were found to be within the Pharmacopoeial limits and showing fair to good flow properties.

Table.3.Post compression parameters of the various batches of the Paliperidone tablets

Formulation	Hardness (kg/cm²)	Thickness (mm)	Weight variation	Friability	Content uniformity%
F1	8.5±0.11	3.56±0.03	99.2±1.2	0.18±0.02	99.17±0.4
F2	7.1±0.52	3.49±0.09	98.3±1.5	0.22±0.05	99.44±0.9
F3	8.5±0.39	3.53±0.05	99.5±1.4	0.43±0.09	98.64±0.2
F4	7.5±0.35	3.61±0.01	99.1±2.4	0.20±0.06	99.2±0.4
F5	8.2±0.14	3.57±0.06	98.8±1.2	0.38±0.09	99.89±0.9
F6	7.5±0.82	3.63±0.07	99.7±2.5	0.12±0.04	99.97±0.6
F7	7.6±0.12	3.62±0.04	98.5±1.7	0.24±0.02	99.24±0.7
F8	7.3±0.92	3.57±0.08	97.6±1.4	0.16±0.04	99.62±0.3
F9	8.5±0.27	3.63±0.04	100.1±1.9	0.45±0.06	99.19±0.3
F10	8.5±0.29	3.55±0.03	99.3±2.8	0.29±0.07	99.73±0.7
F11	7.4±0.60	3.71±0.07	101.2±1.6	0.17±0.07	99.69±0.6
F12	7.2±0.51	3.59±0.06	99.9±1.5	0.19±0.02	99.82±0.8

Tablet thickness: The thicknesses of the tablets were found to be between 3.49±0.09 to 3.71± 0.07 mm for the formulations F1 to F12 as indicated in the table, which is in the acceptable range.

Weight Variation Test: The weight variation of tablets for all the formulations developed F1 to F12 is 101.2±1.6 to 97.6±1.4 mg respectively as indicated in the table. According to pharmacopeia tablets weighing between 100-150mg should not exceed a standard deviation of 5%. So the standard deviation of all the formulation batches did not exceed a SD of 5% hence the tablets comply with standard limits.

Tablet hardness: The hardness of the tablets of different formulations from F1 to F12 varied between 7.1 ± 0.52 to 8.5 ± 0.29 kg/cm^2 as indicated in the table. Generally the hardness varies in the range of 5 to 9 for Matrix tablets. So the formulated batches are within the predetermined limits.

Tablet Friability: The friability of the tablets was found for all the developed formulations from F1 to F12 as 0.12±0.04 to 0.45±0.06% respectively as indicated in the table. Usually more than 1% deviation is not accepted. A very low standard deviation of less than 1% was found in all the formulations. Thus the friability of all the formulations is within the pharmacopoeial limits.

Drug content of Paliperidone tablets: The drug content was estimated in the tablets for all the formulations developed from F1 to F12. The drug content uniformity can be estimated. The drug content for the formulations F1 to F12 are 98.64±0.2 to 99.97±0.6 respectively as indicated in the table which is within the limits.

Table.4.Comparative dissolution data of best formulation (F12)

Time (hr)	Mean % drug dissolved											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	29	14	12	13	46	23	27	24	21	20	9	11
4	52	40	33	31	84	43	54	47	42	36	35	34
8	73	61	57	52	94	52	73	65	61	57	61	58
12	87	82	67	67	99	59	87	76	81	78	78	77
16	98	90	74	74	102	62	98	77	94	92	89	86
20	103	98	78	80	102	67	102	79	101	97	97	91
24	103	103	82	87	103	74	103	81	103	102	101	97

Time(hrs)	F12 (%)	R (%)
0	0	0
1	11	10
4	34	32
8	58	56
12	77	73
16	86	84
20	91	93
24	97	96

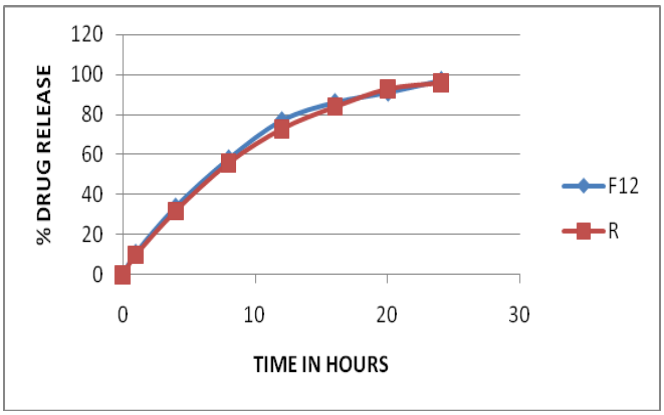

Fig.1.Comparative dissolution profile of best formulation (f12) and reference(R)

The drug dissolution studies were performed for all the formulations developed from F1 to F12.

F12 Formulation was shown best in-vitro drug release profile (97% in 24hrs) compare to other formulations.

Table.5.In-vitro drug release kinetics:

Release Kinetics	Correlation coefficient(R^2) (Reference)	Correlation coefficient(R^2) (F12)
Zero order	0.923	0.912
First order	0.927	0.981
Higuchi	0.986	0.982
Korsmeyer-Peppas	0.987	0.983

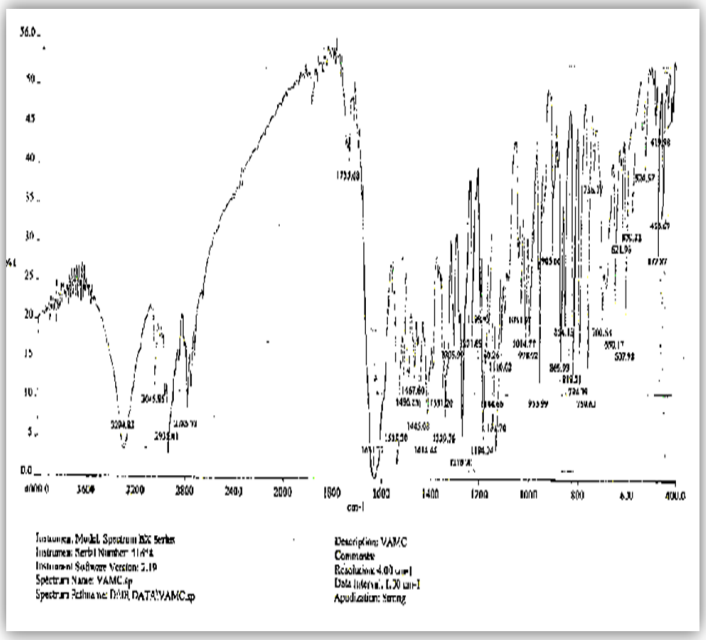

Fig.2. FTIR Spectrum of Paliperidone

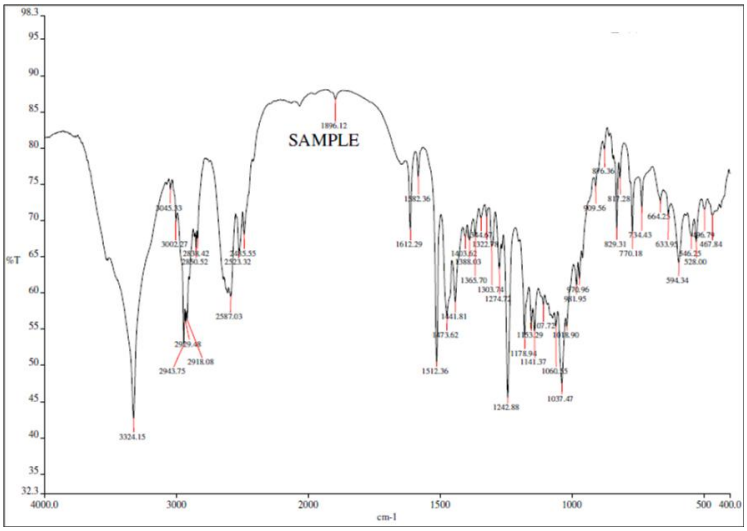

Fig.3. FTIR Spectrum of Paliperidone with HPMC K100M and MCC

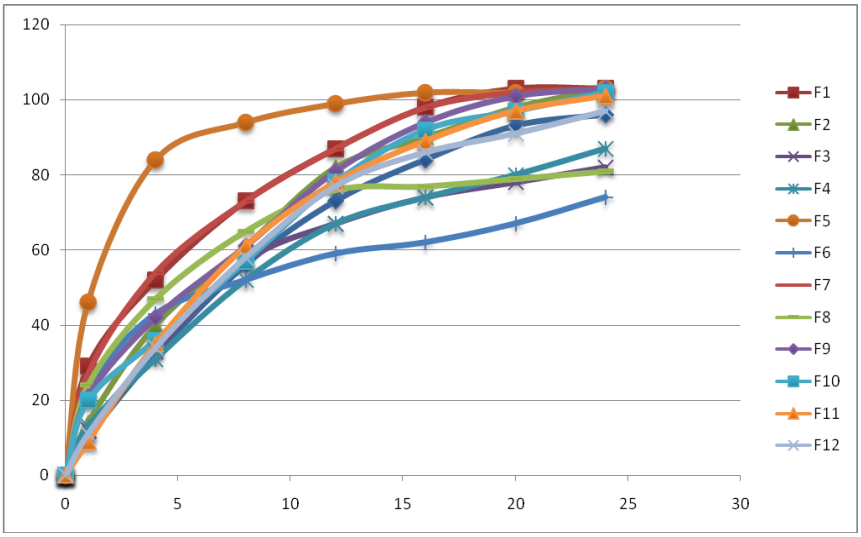

Fig.4.Comparitive release profile of Formulations F1to F12 (Plot of % drug release Vs Time)

DISCUSSION

From the above data comparing the regression values of various kinetic models, it was found that the formulation F12 follows Korsmeyer- Peppas release as the regression value is closed to unity, and regreesion values indicated fairly linearity in the data. The data indicated poor linearity, and less than the value of Korsmeyer - Peppas Plot, when it is plotted according to the first order equation. HPMC K100M, PVP PEO were selected as polymers for the formulation of tablets. Tablets were prepared by direct compression method. 12 different formulations (F1 –F12) were prepared by changing drug polymer (HPMC, PVP and PEO) ratio. The prepared tablets were evaluated by different parameters such as Thickness, Weight variation, Hardness, friability, Content Uniformity and in vitro drug release. Among these formulations were selected and optimized to know the effect of change in surfactant concentration. Again the formulation was evaluated for various parameters and F12 was selected as the best formulation. The best formulation F12 showed a better drug release of 97% over 24 hours. The drug release followed Korsmer- peppas (R^2 = 0.983) and release kinetics best fitted in to Higuchi model.

CONCLUSION

It was concluded that tablets can be promising drug delivery system as it can throughout the GIT and drug in prolonged and controlled passion, so the bioavailability can be increased with reducing dosing frequency. Further invivostudies have to be carried out.

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