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DEVELOPMENT AND EVALUATION OF PAROXETINE HYDROCHLORIDE FAST DISSOLVING TABLETS

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Abstract

Paroxetine Hydrochloride is a potent and selective inhibitor of 5-hydroxytryptamine (5-HT, serotonin) uptake. It is a BCS class – I drug used in the treatment of depression and anxiety disorders. Paroxetine HCl undergoes extensive first-pass metabolism leading to poor bioavailability. The aim of present work is to formulate and evaluate Paroxetine HCl fast dissolving tablets prepared by direct compression method using super disintegrants like sodium starch glycolate, directly compressed lactose, and microcrystalline cellulose as diluents and menthol as sublimating agent. The prepared tablets were evaluated for uniformity of weight, thickness, friability, content uniformity, hardness, disintegration time, wetting time and for in vitro drug release. Further the tablets were characterized by fourier transform infra red spectroscopy. Among all the formulations the tablets prepared by menthol with sodium starch glycolate as super disintegrant containing lactose as diluents showed faster disintegration and rapid drug release.

Key words: *Paroxetine Hydrochloride, sodium starch glycolate, directly compressed lactose, Sublimation.*

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INTRODUCTION:

Fast dissolving dosage forms can be disintegrated, dissolved, or suspended by saliva in the mouth. Fast dissolving tablets are useful in patients, like pediatric, geriatric, bedridden, or mentally disabled, who may face difficulty in swallowing conventional tablets or capsules leading to ineffective therapy, with persistent nausea, sudden episodes of allergic attacks, or coughing for those who have an active life style[1,2]. Fast dissolving tablets are solid dosage form containing medical substances which disintegrate rapidly, usually within few seconds when placed upon tongue requiring no additional water to facilate swallowing[3,4].

Paroxetine is a selective serotonin reuptake inhibitor (SSRI) used in treatment of depression. Paroxetine; {(3S, 4R)-3- [(1,3-benzodioxol-5-vloxy)methyl]–4-(4-urophenyl) piperidine}. Paroxetine is a new generation antidepressant drug. It exerts its antidepressant effect through a selective inhibition for the reuptake of the neurotransmitter serotonin by the presynaptic receptors. Paroxetine is comparable to the tricyclic antidepressants in their clinical efficacy, however, Paroxetine is safer and has greater acceptance by the patients[5]. It is also prescribed in the treatment of related disorders, such as obsessive-compulsive disorder, panic, social phobia, and posttraumatic stress[6]. Paroxetine is devoid of sedative effect and remarkably safe in overdose. Paroxetine takes 5.2 hours to reach the peak plasma concentration,

95% protein binding, with extended half-life (24 hours), that allowed the introduction of formulations for once-daily dosing. These combined qualities made Paroxetine the most widely prescribed antidepressants[7].

In sublimation method, the rapid disintegration of the tablets is achieved by creation of pores in the tablets up on sublimation of volatile components added in the tablets. The saliva will enter these pores and cause the rapid disintegration of the tablets in the oral cavity. The porous structure is responsible for the faster water uptake, Hence it facilitates wicking action in bringing about faster disintegration[8,9].

Direct compression is one of the techniques requires the incorporation of a super disintegrants into the formulation the use or highly. The basic approach used in development of FDT was the use of super disintegrants like cross linked Croscarmellose Sodium, Polyvinyl Pyrrolidone K30, Microcrystalline Cellulose, Crospovidone etc. which provide instantaneous disintegration of tablet after placed on tongue, thereby releasing the drug in saliva. In the present work Paroxetine HCl fast dissolving tablets were prepared by direct compression method using super disintegrants like sodium starch glycolate, directly compressed lactose, and microcrystalline cellulose as diluents and menthol as sublimating agent.

MATERIALS AND METHODS

Paroxetine Hydrochloride a gift sample from Aurbindo labs, Hyderabad, Sodium Starch Glycolate Commercially procured from Loba chemie, Mumbai, menthol and lactose Commercially procured from Loba chemie, Mumbai, Micro Crystaline Cellulose Commercially procured from colorcon chemicals Asia Pvt.Ltd, Mannitol Commercially procured from Qualigens Fine Chemicals, Mumbai, Magnesium Stearate Commercially procured from moly Chemicals, Mumbai, Talc Commercially procured from Loba chemie, Mumbai.

PREPARATION OF FAST DISSOLVING TABLETS BY SUBLIMATION METHOD:

Fast disintegrating tablets of Paroxetine hydrochloride were prepared by using sublimation method. The super disintegrating agent such as sodium starch

glycolate was added in varying concentrations. Accurately weighed quantity of Paroxetine hydrochloride, subliming agents (menthol), super disintegrating agent, directly compressed lactose (DCL21), micro crystalline cellulose and dicalcium phosphate and mannitol were mixed and passed through the sieve # 44. Finally, magnesium stearate and talc were added as lubricating agent. The powder mixture was subjected to compression into tablet using a single-punch tablet machine. After compression tablets were heated in a hot air oven at 60°C until constant weight was obtained to ensure the complete removal of volatilizable component to make the tablet porous.

EVALUATION OF PREPARED FAST DISSOLVING TABLETS

Physical parameters such as weight variation, hardness, friability and disintegration were evaluated for prepared tablets[9]. The prepared fast dissolving tablets were future evaluated for physical parameters like drug content, wetting time, water absorption ratio, and moisture uptake studies and for invitro dissolution studies.

The moisture uptake study was carried out by keeping 10 tablets along with calcium chloride in a desiccators maintained at 37˚C for 24hrs to ensure complete drying of the tablets. The tablets were then weighed and exposed to 75% RH, at room temperature for 2 weeks. The required humidity can be achieved by keeping saturated sodium chloride solution in the desiccators for 24hrs. The tablets are reweighed and the percentage increase in weight was recorded. If the moisture uptake tendency of a product is high, it requires special dehumidified area for manufacturing and packing of the tablets [10].

Wetting time is carries out by taking 5 circular tissue papers of 10cm diameter were placed in a petridish with 10cm diameter. 10mL of water containing Amaranth, water soluble dye was added to the petridish. One tablet was carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet was noted ad wetting time [11].

Disintegration times of fast dissolving tablets were carried out by the method given by Gohl. For this a petridish was filled with 10mL of water and the tablet was carefully placed in the centre of petridish and the time taken for the tablet to completely disintegrate into fine particles was noted.

In Vitro **Dissolution:** Dissolution studies on each formulation were performed in a calibrated 8 station test apparatus (LAB INDIA) equipped with paddles (USP apparatus II method) employing 900ml of 0.1N HCl as a dissolution medium. The paddles were operated at a 50 rpm and the temperature was maintained at 37±0.5°C throughout the experiment. Samples were withdrawn at regular intervals for 30 min and replaced with equal volume of same dissolution medium to maintain the constant volume throughout the experiment. Samples withdrawn at various time intervals were suitably diluted with same dissolution medium and the amount of drug released was estimated by ELICO double beam spectrophotometer at 240nm. The dissolution studies on each formulation were conducted in triplicate.

CHARACTERIZATION OF FAST DISSOLVING TABLETS

FTIR Spectral Analysis:

Infrared spectra of drug and excipients were recorded by KBr pellet method using fourier transform infrared spectrophotometer (BRUKER 8400S). A base line correction was made using dried potassium bromide and then spectra of dried mixtures of drug and inclusion complexes with potassium bromide were recorded. The samples were prepared by KBr pellet press method. The spectra are shown in the figures 4-6.

RESULTS AND DISCUSSION

Fast dissolving tablets of Paroxetine hydrochloride were prepared by sublimation method using superdisintegrants like sodium starch glycolate and menthol as sublimating agents in different concentrations i.e., 20 and 25%.the compositions of various tablet formulations are given in table 1.

All batches of tablets were compressed under identical conditions to minimize the processing variables. Then the compressed fast dissolving tablets were further evaluated for physical parameters such as weight uniformity, hardness, friability and drug content. These studies revealed that all the tablet formulations were found to be stable and meeting I.P specified limits weight uniformity, friability and drug content. The hardness of all the tablet formulations was in the range of 3.0 to 3.5 kg/cm^2. Weight uniformity of all the tablet formulations were in the range of 250 ± 3 mg/tablet. Friability losses of all the tablet formulations were negligible and were in the range of 0.1 to 0.2%. Drug content estimated for all the tablet formulations was highly uniform with less than 2.5% variation**.**

Dissolution studies were performed on all the tablet formulations by using U.S.P paddle method (apparatus II).based on the data obtained from the dissolution studies, various parameters such as $T_{50,}$ DE_{30}% , first order and zero order release rate constants were estimated. The dissolution parameters such as $T_{50,}$ was measured directly from the dissolution profiles curves and DE_{30}% was estimated by employing trapezoidal rule to the dissolution profiles. The dissolution profiles of Paroxetine HCI fast dissolving tablets were shown in figure 1,2, and 3. The *in vitro* dissolution and kinetic parameters were given in table 2 and 3**.** The drug from various tablet formulations were released at a faster rate compared to pure drug. Formulations prepared by sodium starch glycolate (SSG) and lactose as diluent released the drug at faster rate than other FDTs contain Micro crystalline cellulose (MCC) and Dicalcium phosphate (DCP) as diluents. Formulation PF-3 and PF-6 prepared by Sublimation method using SSG as superdisintegrant found to release≈ 98% in 30 min was suitable as fast dissolving tablet. IR studies of Paroxetine HCI formulations were done to know any drug and excipient interactions. The results indicated that there were no drug and excipient interactions.

CONCLUSION

From the present study, it is concluded that the tablets of Paroxetine hydrochloride prepared by sublimation technique using menthol as sublimating agent are suitable for FDT. Sublimation technique would be an alternative approach to use of more expensive adjuvant and sophisticated instruments in the formulation of FDT. The prepared tablet gives benefit in terms of patient compliance, rapid onset of action, increased bio-availability, low side effect and good stability which make these tablets popular as a dosage form for the treatment of depression and anxiety disorders.

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Table 1: Compositions of Paroxetine Hydrochloride Fast Dissolving Tablets

S.No	Ingredients (mg)	PF1	PF2	PF3	PF4	PF5	PF6	PF7	PF8	PF9
1	Paroxetine hydrochloride	20	20	20	20	20	20	20	20	20
2	Sodiumstarch glycolate	50	62.5	75	50	62.5	75	50	62.5	75
3	DCL	91.5	66.5	41.5	----	---	---	----	----	----
4	MCC	-----	-----	----	91.5	66.5	41.5	----	----	-----
5	DCP	-----	-----	------	----	----	-----	91.5	66.5	41.5
6	Mannitol	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5
7	Magnesium stearate	1	1	1	1	1	1	1	1	1
8	Menthol	50	62.5	75	50	62.5	75	50	62.5	75
9	Total	250	250	250	250	250	250	250	250	250

Table 2: Physical Parameters of Paroxetine HCl Fast Dissolving Tablets

S.No	Formu-lation	Weight uniformity (mg)	Hardness (kg/cm^2)	Friability (%)loss	Wetting time(sec)	Disintegration time (min	Drug content
1	PF1	250±0.3	3.2	0.16	51	2.15	19
2	PF2	248±0.3	3.5	0.21	56	2.15	19.3
3	PF3	250±0.3	3.4	0.18	45	2.40	20
4	PF4	248±0.4	3.5	0.20	60	3.30	19.0
5	PF5	248±0.3	3.0	0.19	54	3.15	19.8
6	PF6	251±0.3	3.2	0.16	60	3.00	18.9
7	PF7	250±0.4	3.4	0.17	70	3.20	19
8	PF8	248±0.3	3.0	0.19	75	4.15	19.2
9	PF9	249±0.4	3.1	0.18	86	4.15	19.5

Table 3: *In vitro* Dissolution Parameters of Paroxetine Hydrochloride Fast Dissolving Tablets

Formulation	T_{50}%	DE_{30}%	Zero Order Constant		First Order Constant	
			K	R^2	K(min^{-1})	K(min^{-1})
PF1	9±0.2	80.0±0.4	0.520	0.531	0.113	0.113
PF2	8±0.4	81.2±0.5	0.618	0.466	0.016	0.016
PF3	2±0.4	74.3±0.2	0.514	0.404	0.018	0.018
PF4	6±0.4	78.5±0.5	0.612	0. 374	0.021	0.021
PF5	6±0.5	80.7±03	0.574	0.298	0.027	0.027
PF6	3±0.3	86.2±0.4	0.587	0.565	0.017	0.017
PF7	8±0.2	78.0±0.4	0.589	0.549	0.019	0.019
PF8	6±0.5	76.5±0.5	0.561	0.620	0.023	0.521
PF9	8±0.4	80.4±0.2	0.653	0.694	0.026	0.582

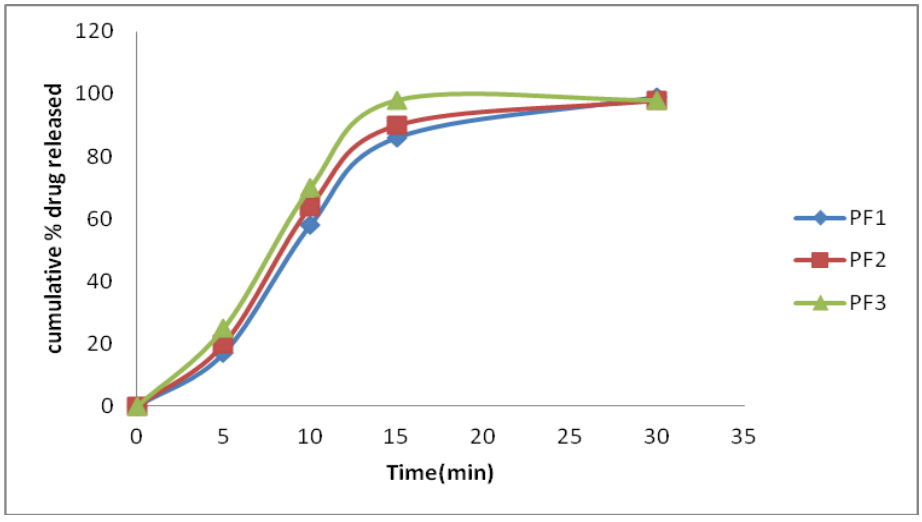

Figure 1: Dissolution Profiles of Paroxetine Hydrochloride Fast Dissolving Tablets

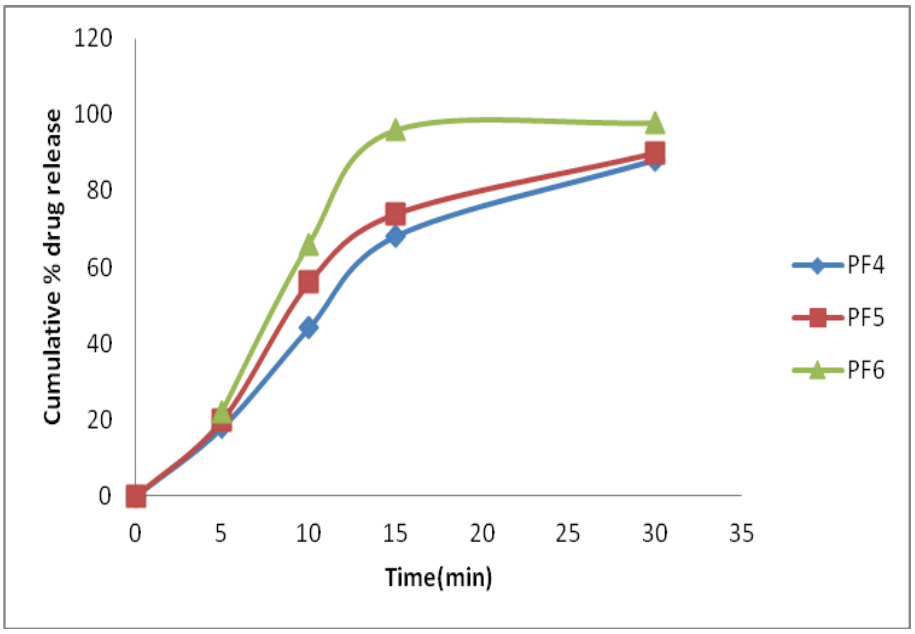

Figure 2: Dissolution Profiles of Paroxetine Hydrochloride Fast Dissolving Tablets

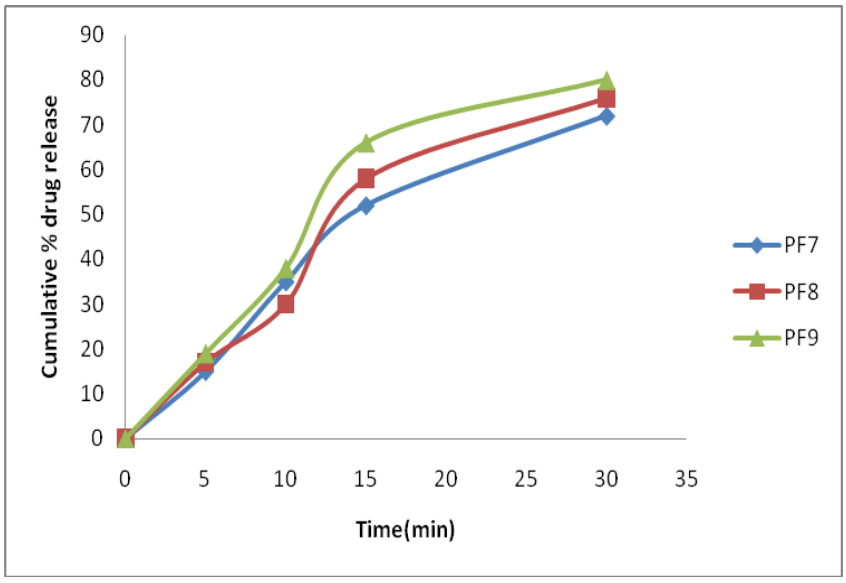

Figure 3: Dissolution Profiles of Paroxetine Hydrochloride Fast Dissolving Tablets

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