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Formulation and evaluation of floating tablets of Tapentadol HCl by direct compression method by using different swellable polymers and effervescent agents

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ABSTRACT

Floating tablets of Tapentadol Hcl were formulated by using swellabale polymers like carbomer, hypermellose, hydroxyl propyl cellulose, and gas forming agents like sodium bicarbonate. Drug excipient compatibility studies were conducted. Drug release profile was also studied. Effect of polymers on drug release kinetics was studied.

1. INTRODUCTION

Floating drug delivery systems have 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.

Tapentadol is a centrally-acting synthetic analgesic. Although its exact mechanism is unknown, analgesic efficacy is thought to be due to mu-opioid agonist activity and the inhibition of norepinephrine reuptake. Tapentadol is isolated as the hydrochloride salt. All polymorphic forms of tapentadol are freely soluble within the physiological pH range. Tapentadol is designated as Class 1 (high permeability, high solubility) in The Biopharmaceutics Classification System.

Tapentadol is a centrally-acting synthetic analgesic. It is 18 times less potent than morphine in binding to the human mu-opioid receptor and is 2–3 times less potent in producing analgesia in animal models. Tapentadol has been shown to inhibit norepinephrine reuptake in the brains of rats resulting in increased norepinephrine concentrations. In preclinical models, the analgesic activity due to the mu-opioid receptor agonist activity of tapentadol can be antagonized by selective mu-opioid antagonists (e.g., naloxone), whereas the norepinephrine reuptake inhibition is sensitive to norepinephrine modulators. Tapentadol exerts its analgesic effects without a pharmacologically active metabolite.

Mean absolute bioavailability after single-dose administration (fasting) is approximately 32% due to extensive first-pass metabolism. Maximum serum concentrations of tapentadol are typically observed at around 1.25 hours after dosing. Dose-proportional increases in the Cmax and AUC values of tapentadol have been observed over the 50 to 150 mg dose range. Multiple (every 6 hour) dose study with doses ranging from 75 to 175 mg tapentadol showed a mean accumulation factor of 1.6 for the parent drug and 1.8 for the major metabolite tapentadol-O-glucuronide, which are primarily determined by the dosing interval and apparent half-life of tapentadol and its metabolite.

Carbomer polymers are formed from repeating units of acrylic acid. Carbomers are synthetic high-molecular-weight polymers of acrylic acid that are crosslinked with either allyl sucrose or allyl ethers of pentaerythritol. They contain between 52% and 68% of carboxylic acid (COOH) groups calculated on the dry basis.

Carbomers are used in liquid or semisolid pharmaceutical formulations as rheology modifiers. Formulations include creams, gels, lotions and ointments for use in ophthalmic, rectal,topical and vaginal preparations.

The PhEur 6.3 describes hypromellose as a partlyO-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in

viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 20^0C. Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating and as a matrix for use in extended release tablet formulations. Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25–5.0%.Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets.

2. MATERIALS AND METHODS

Tapentadol HCL, A gift sample from Bio-Leo Analytical labs, Hyderabad, all other chemicals and reagents were purchased form SD fine chemicals, Mumbai.

Formulation development of floating Tapentadol HCl tablets: A series of formulation design were prepared and tabulated in table 1. Various formulations of floating matrix tablets were developed for Tapentadol HCL using polymers like HPMCK4M, HPMCK15M HPMCK100, HPC, and Carbapol971P. Sodium bicarbonate was selected as gas generating agent, Manitol as diluents, Magnesium stearate as lubricant, talc as glidant.

Table.1.Formulation chart from F1-F15

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Tependadol HCl	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
HPMC K4M	15	30	45												
HPMC K100				15	30	45									
HPMC K15M							15	30	45						
HPC										15	30	45			
Carbopol 971P													15	30	45
Mannitol	58	43	28	58	43	28	58	43	28	58	43	28	58	43	28
$NaHCO_3$	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
Mg.stearate	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Talc	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Total weight of tablet	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150

Swelling Study: Swelling of the polymers can be measured by their ability to absorb water and swell. Swelling characteristics of the tablets were expressed in terms of water uptake. Swelling of hydrophilic polymer such as Hydroxy Propyl Methyl Cellulose greatly depends upon the contents of the stomach and the osmolarity of the medium. These eventually influences the release, slowing action and the residence time. After a selected time intervals, the tablets were withdrawn, blotted to remove excess water and weighed. One tablet from each formulation was kept in a beaker containing 200 ml of pH 0.1N HCL. At the end of 1 hour, the tablet was withdrawn and weighed. This process was repeated at several intervals. % weight gain by the tablet was calculated by formula.

$$W_U = \frac{(W_1 - W_0)}{W_0} \times 100$$

Wt = Weight of dosage form at time t.

W0 = Initial weight of dosage form.

In-vitro buoyancy studies: The in-vitro buoyancy was determined by floating lag time as per the method described by Rosa et al., 1994. The prepared formulations were placed in a 100 ml glass beaker containing 0.1N HCL.

In-vitro Drug release studies: The drug release studies were carried out using six dissolution apparatus USP type II. The dissolution medium used was 900ml of 0.1N HCL 37°C, 50rpm. At specific time intervals of 1, 2, 4, 6, 8, 10, 12 and16hr respectively. An aliquot of 5ml were withdrawn and analyzed by UV visible spectrophotometer at the respective λmax value 275nm after suitable dilution against suitable blank. The withdrawn volume was replaced with an equal volume of fresh medium.

3. RESULTS AND DISCUSSION

Swelling Studies: The swelling behavior of drug loaded tablets of weight 150 mg and diameter 6.98mm and thickness 3.12 mm were studied. The swelling behavior

of tablets were done by measuring radial swelling in 0.1 N HCl medium. Assessment of the swelling behavior was done by measuring radial swelling. Among all the formulations F7, F13 were shown high radial swelling. (98.02±0.04%, 98.4±0.01%).In case of F9,F3 were shown low radial swelling (75.54±0.04%,76.5±0.02%).This swelling behavior indicates that with the increase of concentration of polymer, radial swelling index decreased.

In-vitro Buoyancy Studies: All the film formulations F1 to F15 were subjected to in-vitro buoyancy studies at agitation conditions for evaluation of buoyancy lag time and duration of floating characteristics. F3, F9, F12, and F15 have shown excellent buoyancy characteristics by maintaining their integrity more than 14 hours, it shows the consistent floating ability of the respective polymers through the formation of hydrogels upon wetting.

In-vitro Drug Release Studies: The in-vitro drug release studies for the formulations F1toF15 were carried out using six basket dissolution apparatus USP type II. The dissolution medium used was 900ml of 0.1N HCl at 37°C, 50rpm. In the dissolution profile, the concentration of polymer increases the drug release profile decreases.

The formulation F1, F4, F7, F10 and F13 having 10% concentration of HPMCk4m, k100, k15m, HPC and Carbopol971P showing 96.18, 94.77, 97.01, 95.52 and 97.41 % drug release with respect of time. The formulation F2, F5, F8, F11, and F14 having 20% concentration of Polymer showing 96.56%, 95.34%,98.11%, 97.20% and 96.26% drug release with respect of time. The formulation F3, F6, F9, F12, F15 having 30% concentration of polymer showing 96.74%, 96.26%, 98.5%, 98.13% and 97.64% drug release with respect of time. The Formulation F9 has shown good release, but 98.5% drug release was found at the end of 16 hours. In formulation F9 the polymers were used are HPMCK15M (30%) was used to improve the drug release of tablets.

Table.2.Comparative drug release profile of Tapendol Hcl floating tablets

Time (hours)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
1	27.23	22.54	18.03	37.42	24.44	19.6	34.32	28.73	17.16	23.88	21.26	16.23	28.37	25.73	18.02
2	41.9	35.12	27.8	61.94	35.82	32.46	55.22	45.9	26.86	32.46	28.73	24.99	56.6	49.46	29.86
4	66.12	50.34	37.76	94.77	49.44	50.56	75.74	61.94	36.94	47.76	43.65	33.76	79.59	72.08	41.19
6	91.86	63.87	51.47		70.89	65.67	89.18	73.5	48.88	72.57	61.56	51.11	97.41	87.15	69.47
8	96.18	77.02	64.46		85.82	78.36	97.01	85.07	60.44	95.52	87.31	66.23		96.26	81.64
10		96.56	78.9		95.34	89.55		90.2	69.4		97.2	87.87			97.77
12			91.86			96.26		98.4	78.54			98.13			
14			96.74						87.31						
16									98.5						

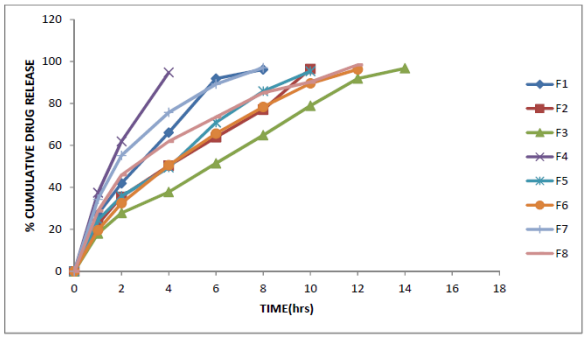

Figure.1.Comparitive drug release F1-F8

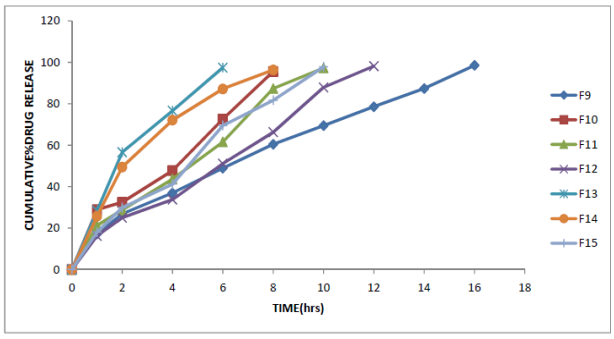

Figure.2.Comparitive drug release F9-F15

4. CONCLUSION

In conclusion based on the results that is pre-compression parameters, physical chemical properties swelling studies buoyancy studies and in vitro drug release studies it was found at that the formulation F9 show excellent drug release of 98.5% for 16 hours and shows buoyancy for 18 hour, so formulation F9 were selected for best optimized Tapenpacol Hcl effervescent floating tablet formulation.

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