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Research Article

Formulation, development and *in vitro* evaluation of floating tablet of tramadol hydrochloride

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ABSTRACT

Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the 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. Tramadol Hydrochloride effervescent sustained release tablets were developed in eight different formulations (TF1 to TF8) by employing different grades of polymers and effervescent agents such as sodium bicarbonate and citric acid. The formulations were evaluated for various physical parameters, dissolution parameters and drug released mechanisms. TF8 formulation showed maximum floating time of 12 hours and gave slow and maximum drug release of Tramadol Hydrochloride spread over 12 hours and whereas Tramadol Hydrochloride released from marketed tablet was rapid and maximum within 8.3 hours.

Keywords: Tramadol Hydrochloride, In Vitro Evaluation, Polymers.

INTRODUCTION

The concept of floating drug delivery system offers experiencing engaging or choking by some person while swallowing medicinal pills. The researcher suggested that difficulty could overcome by providing pills having a density of less than 1.0g/ml. So that pill will float on water surface since then several approaches have been proposed for ideal floating delivery system. This buoyant delivery system includes hollow microspheres powder granules, tablet, capsules and laminated films.

Effervescent floating drug delivery systems generate gas (CO₂), thus reduce the density of the system and remain buoyant in the stomach for a

prolonged period of time and released the drug slowly at a desired rate. Depending on the mechanism of buoyancy two distinctly different methods viz. effervescent and non effervescent system have been used in the development of floating drug delivery systems (FDDS).

In present work, effervescent floating tablets of different formulation were developed with an objective of achieving above 12 hrs floating and drug release time and the effervescent floating tablet was compared with marketed formulation of Amlodipine besylate for drug released time.

MATERIALS AND METHODS

Materials

Tramadol Hydrochloride, Citric Acid and Sodium Bicarbonate, HPMC and EC, Ethanol and methanol, All other Excipients used in our work were of analytical grade.

Preparation of Floating Tablets of Tramadol Hydrochloride

Effervescent Floating tablets containing Tramadol Hydrochloride were prepared by direct compression technique using varying concentrations of different grades of polymers with Sodium bicarbonate and citric acid. All the ingredients were accurately weighed and passed through different mesh sieves accordingly. Then, except Magnesium stearate all other ingredients were blended uniformly in glass mortar. After sufficient mixing of drug as well as other components, Magnesium stearate was added, as post lubricant, and further mixed for additional 2-3 minutes. The tablets were compressed using rotary tablet machine. The weights of the tablets were kept constant for all formulation.

Evaluation of effervescent floating tablet formulations

Evaluation of Tramadol Hydrochloride Granules

The flow properties of granules (before compression) were characterized in terms of angle of repose, tapped density, bulk density, Carr's index and Hausner ratio. Physical evaluation of famotidine floating tablets Two tablets from each formulation were randomly selected and organoleptic properties such as colour, odour, taste, and shape were evaluated. Thickness and diameter of ten tablets were measured using vernier calipers. The prepared floating tablets were evaluated for uniformity of weight using 20 tablets, hardness (Monsanto tester), friability using 10 tablets (Roche type friabilator).

Determination of Swelling Index

The swelling index of tablets was determined in 0.1N HCl (pH 1.2) at room temperature. The swollen weight of the tablet was determined at predefined time intervals over a period of 24 h. The swelling index (SI), expressed as a percentage.

RESULTS AND DISCUSSION

Floating tablets Tramadol Hydrochloride were developed to increase the gastric residence time of the drug, so that they can be retained in stomach for longer time and help in controlled release of drug to minimum 12 h. The tablets were made using different gel forming polymers such as HPMC along with effervescent agent sodium bicarbonate and citric acid to optimize the drug content, in vitro buoyancy, swelling index and in vitro drug dissolution studies. The selection of viscosity grade of a polymer is an important consideration in the formulation of tablet. All the formulations were prepared by direct compression method. When a combination of gas entrapment as well as controlled release system is there, the use of disintegrating agent is important which does not quickly break the matrix and allows slow disintegration of the swollen matrix. PVP K30 in an optimized concentration (15mg/tablet) was employed for such unique disintegration properties. Talc and magnesium stearate were employed for their glidant and lubricant property. The prepared tablets of all the formulations were evaluated for pre compression parameters like angle of repose, bulk and tapped density and compressibility index and physical characters like tablet hardness, friability, weight variation buoyancy lag time, total floating time, assay, in-vitro drug release. The main aim was to optimize the formulation for 14 hours in-vitro release and total floating time to more than 12 hours.

Pre compression parameters of Tramadol Hydrochloride granules

The formulations showed good flow property and compressibility index (Table 2). Angle of repose ranged from 26.35 to 28.46, Hausner ratio ranged from 0.718 to 0.730 and the compressibility index ranged from 27.30 to 38.23. The bulk density and tapped density of the prepared granules ranged from 0.576 ± 0.002 to 0.593 ± 0.008 and 0.728 ± 0.005 to 0.790 ± 0.008 respectively. The results of angle of repose indicates good flow property of the granules and the value of compressibility index further showed support for the flow property.

Post compression parameters of Tramadol Hydrochloride tablets

The shape of the tablets of all formulations remained off white, smooth; flat faced circular with no visible cracks. The thickness of tablets was

measured by vernier calipers and was ranged between 3.53 ± 0.05 to 4.05 ± 0.05 mm. The hardness of the tablets was measured by Monsanto tester (Monsanto hardness tester) and was in between 4.5 to 5.3 kg/cm². The friability was measured by Friabilator (Electronics India, Himachal Pradesh) and was found to be 0.16 ± 0.04 to 0.58 ± 0.10 %, which is an indication of satisfactory mechanical resistance of the tablets. The drug content estimations showed values in the range of 97.20 ± 0.34 to 99.60 ± 1.39 % which reflects good uniformity in drug content among different formulations. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeial limits of $\pm 5\%$ of the weight.

All the formulations showed values within the prescribed limits for tests like hardness, friability and weight variation which indicate that the prepared tablets are of standard quality.

Buoyancy lag time (BLT) and total floating time (TFT)

Effervescent floating tablet of different formulations were noted, where TF1 BLT of 25 sec and TFT of >8 hours, TF2 BLT of 35 sec and TFT of >10 hours, BLT of 56 sec and TFT of >12 hours, TF4 BLT of 75 sec and TFT of >12 hours, TF5 BLT of 60 sec and TFT of >12 hours, TTF6 BLT of 80 sec and TFT of >12 hours, TF7 BLT of 110 sec and TFT of >12 hours, TTF8 BLT of 125 sec and TFT of >12 hours, With reference to buoyancy studies results it can be concluded that the batch containing HPMC polymers showed good buoyancy lag time (BLT) and total floating time (TFT). Formulation TTF8 containing Ethyl cellulose showed good BLT of 110 sec and TFT of more than 24 hrs.

In vitro dissolution studies

In vitro dissolution studies of all the formulations are shown in Table 5 and figure 1. It was observed that the type of polymer influences the drug release pattern. A significantly higher rate and extent of drug release was observed from the batches based on EC. Drug release from HPMC was lesser owing to its high viscosity and also due to less permeability of water to HPMC. Moreover the HPMC containing tablets TF7-TTF8 could not bear their matrix shape until 14 h and drug released before 14 h. As expected, the drug release rate was dependent on the viscosity grade and the concentration of the polymer used. This controlled release of drug from TTF8 could be attributed to the formation of a thick gel structure that delays drug release from the tablet matrix. Thus a formulation TF7 was selected as the promising formulation, containing combination of sodium bicarbonate (15 mg) and citric acid (30 mg) with EC (50 mg), as it achieved optimum in vitro buoyancy, floatability of more than 12 hrs as well as controlled and sustained in vitro drug release.

Stability study of optimized formulation (TF7)

The optimized floating tablets (TF7) were selected for stability study on the basis of in vitro drug dissolution studies. The tablets were investigated at 40°C/75% RH for 3 months. From the data, the formulation is found to be stable under the conditions mentioned above since there was minimum significant change in the percentage amount of drug release. Thus, it was found that the floating tablets of Tramadol Hydrochloride (TF7) were stable under these storage conditions for at least 3 months.

Various formulation of floating tablet of tramadol hydrochloride

Excipients	TF1	TF2	TF3	TF4	TF5	TF6	TF7	TF8
Tramadol Hydrochloride	250	250	250	250	250	250	250	250
HPMC	50	50	50	50	-	-	-	-
Ethyl cellulose	-	-	-	-	50	50	50	50
PVP K30	15	15	15	15	15	15	15	15
Citric acid	25	20	30	20	25	20	30	20
Sodium bicarbonate	20	25	15	20	20	25	15	20
Magnesium stearate	10	10	10	10	10	10	10	10
Talc	20	15	25	25	20	15	25	25
PEG	10	10	10	10	10	10	10	10

Results of physical parameters of floating tablet of tramadol hydrochloride

Material	Angle of repose (Degree)	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index	Hausner ratio
TF1	28.31	0.582±0.002	0.732±0.007	27.33±0.73	0.721±0.01
TF2	26.35	0.581±0.008	0.730±0.006	28.33±0.72	0.723±0.01
TF3	27.82	0.576±0.002	0.728±0.005	27.30±0.68	0.720±0.01
TF4	27.69	0.570±0.007	0.729±0.003	29.30±0.65	0.726±0.03
TF5	28.30	0.580±0.003	0.735±0.004	30.30±0.61	0.730±0.04
TTF6	29.28	0.585±0.003	0.732±0.006	32.80±0.64	0.728±0.06
TF7	28.46	0.582±0.004	0.742±0.003	36.24±0.70	0.720±0.03
TTF8	28.04	0.582±0.006	0.740±0.008	38.23±0.61	0.718±0.01

Results of post compression properties of tramadol hydrochloride

Formulation code	Thickness (mm)	Hardness /cm ²	Weight variation (mg)	Friability (%)	Drug content (%)
TF1	3.53±0.05	4.8	328.19± 2.94	0.58 ± 0.10	98.33± 0.92
TF2	3.94± 0.10	4.4	332.18 ± 3.77	0.51 ± 0.08	97.20 ± 0.34
TF3	3.96± 0.05	4.5	335.33 ± 1.50	0.38 ± 0.12	99.60 ± 1.39
TF4	3.95± 0.05	4.7	336.30 ± 3.30	0.16 ± 0.04	98.14 ± 1.69
TF5	3.93± 0.10	5.2	327.13 ± 2.83	0.31 ± 0.07	99.21 ± 1.07
TTF6	4.03± 0.06	5.3	332.16 ± 2.33	0.27 ± 0.05	99.50± 1.81
TF7	4.05± 0.05	4.8	338.18 ± 3.11	0.29 ± 0.08	99.34 ± 0.37
TTF8	3.98± 0.05	4.5	327.04 ± 2.56	0.34 ± 0.12	98.31± 0.91

Results of In vitro buoyancy study of Tramadol Hydrochloride

Formulation Code	Buoyancy lag times (sec)	Total Floating Time (hrs)
TF1	25s	>8
TF2	35s	>10
TF3	56s	>12
TF4	75s	>12
TF5	60s	>12
TTF6	80s	>12
TF7	110s	>12
TTF8	125s	>12

In vitro Dissolution profile of batches TF1-TF4

Time (hr)	% of Drug Release							
	TF1	TF2	TF3	TF4	TF5	TTF6	TF7	TTF8
1	08.23	07.14	07.24	08.23	07.23	07.45	08.32	07.26
2	12.32	10.23	11.45	10.45	10.45	11.23	12.23	11.87
4	26.23	22.42	24.23	23.76	31.23	38.23	32.13	26.28
8	42.45	40.32	45.23	44.23	48.23	46.32	47.14	38.21
10	76.34	66.11	72.21	65.71	68.34	67.02	71.13	68.24
12	82.23	77.33	81.11	82.34	84.23	88.13	91.23	89.12
14	98.32	97.13	95.13	98.35	99.12	99.13	99.56	99.25

In-vitro drug release profile of optimized formulation during stability study

Product code	Temperature	In-vitro % Drug release profile		
		At 2 weeks	At 3 weeks	At 4 weeks
TF7	4 ⁰ c	97.7	97.04	97.43
	25 ⁰ c	98.63	98.34	98.14
	40 ⁰ c	98.67	98.34	98.23
	50 ⁰ c	98.69	98.47	98.03

CONCLUSION

This study discusses the preparation of floating tablets of Tramadol Hydrochloride. The effervescent-based floating drug delivery was a promising approach to achieve in vitro buoyancy. The addition of polymer HPMC, EC and gas-generating agent sodium bicarbonate was essential to achieve in vitro buoyancy. Addition of citric acid, to achieve buoyancy under the elevated pH of the stomach, caused an enhancement in drug release. The type of polymer affects the drug release rate and the mechanism. Polymer swelling is crucial in determining the drug release rate and is also

important for flotation. A lesser FLT and a prolonged floating duration could be achieved by varying the amount of effervescent and using different polymer combinations. The in vitro drug release profiles obtained for tablets (TF7) showed a prolonged floating duration (> 12hrs) which was a controlled release characteristic (99.58%) for 14 h. Good stability was observed for 3 months during stability studies. Since the formulation showed sufficient release for prolonged period, the dose can be reduced and possible incomplete absorption of the drug can be avoided.

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