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Research Article

Formulation and *in vitro* evaluation of gastro retentive drug delivery system of tramadol hydrochloride

Ravi M*[1] and Narayanan N[2]

[1]Department of Pharmaceutics, Karpagam University, Coimbatore – 641021, Tamil Nadu, India
[2]Department of Pharmaceutics, Jaya College of Pharmacy, Chennai, Tamil Nadu, India

ABSTRACT

Tramadol hydrochloride is a centrally acting synthetic opioid analgesic used in treatment of moderate to severe pain. Tramadol is chemically (1*R*,2*R*)-*rel*-2-[(dimethylamino)methyl]- 1-(3-methohxyphenyl) cyclohexanol. Tramadol Hcl Floating tablet containing tramadol HCl were prepared to have gastroretention in the upper region of stomach with objective of prolongation of the drug release at this region with aim of prolongation of residence time by the candidate due to its low half life with severity of the existing pain. In the present study the dosage forms of floating drug delivery system is tried with different excipients with different grades of polymer of hypromellose like HPMC K 4M, HPMC K 15 M and HPMC K 100 M with varying proportion of disintegrating agent and superdisintegrant along with the gas generating agent such as Sodium bicarbonate. Thus prepared batches of different formulations were subjected for its release kinetics fitted with different kinetic equations the percentage drug release and the effect of superdisintegrant was found that the tramadol Hcl floating tablet is a promising approach as it can lead to decrease in the frequency of administration and increase the residence time in the stomach.

Keywords: Tramadol HCl; Floating drug delivery; Gastro-retentive delivery; Super-disintegrant.

INTRODUCTION

Since time immemorial there is a struggle to find out suitable oral drug delivery system to have slow, sustained release at specific site to have good therapeutic effect with minimum side effect, one such approach leads to formulate site specific drug delivery like colon specific, enteric coating and bucccal e.t.c. The present investigations aims at designing of gastro retentive drug delivery via floatation of drug particles through single dosage form after disintegration. Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation etc. Oral sustained drug delivery formulations show some limitations connected with the gastric emptying time. Variable and too rapid gastrointestinal transit could result in incomplete drug release from the device into the absorption window leading to diminished efficacy of the administered dose. It is evident from the recent research and patent literature that an increased interest in novel dosage forms that are retained in the stomach for a prolonged and predictable period of time exists today.

* Corresponding Author
Email: nravipharma@gmail.com
Contact: +91-7842735254
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Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. One of such difficulties is the ability to confine the dosage form in the desired area of the gastrointestinal tract. To overcome this physiological problem, several drug delivery systems with prolonged gastric retention time have been investigated. Attempts are being made to develop a controlled drug delivery system that can provide therapeutically effective plasma drug concentration levels for longer durations, thereby reducing the dosing frequency and minimizing fluctuations in plasma drug concentration at steady state by delivering drug in a controlled and reproducible manner (Hirtz J. et al. 1985). Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability reduces drug waste and improves solubility of drugs that are less soluble in high pH environment. Gastric retention to provide new therapeutic possibilities and substantial benefits from patients. The controlled gastric retention of solid dosage forms may be achieved by the mechanism of muco adhesion (Ponchel G et al., 1998, Lenaerts VM et al.,1990) floatation, sedimentation, expansion, modified shape systems or by the administration of pharmacological agents (Groning et al.,1984,1989) that delaying gastric emptying. Based on these approaches,

Table 1: Formulation Chart from F1 to F25

S.No	Ingredients (mg)	GRFT1	GRFT2	GRFT3	GRFT4	GRFT5	GRFT6	GRFT7	GRFT8	GRFT9
1	Tramadol	100	100	100	100	100	100	100	100	100
2	HPMC K4M	30	30	30	30	30	30	30	30	30
3	Crosspovidon	8	8	8	_	_	_	_	_	_
4	SSG	_	_	_	8	8	8	_	_	_
5	CCS	_	_	_	_	_	_	8	8	8
6	Sodium bi carbonate	10	20	30	10	20	30	10	20	30
7	MCC PH 101	48	48	48	48	48	48	48	48	48
8	Magnesium stearate	2	2	2	2	2	2	2	2	2
9	Aerosil	2	2	2	2	2	2	2	2	2

Table 2: Formulation chart (GRFT10 to GRF18)

S.No	Ingredients (mg)	GRFT10	GRFT11	GRFT12	GRFT13	GRFT14	GRFT15	GRFT16	GRFT17	GRFT18
1	Tramadol	100	100	100	100	100	100	100	100	100
2	HPMCK15M	30	30	30	30	30	30	30	30	30
3	Cross povidone	8	8	8	--	--	--	--	--	--
4	SSG	--	--	--	8	8	8	--	--	--
5	CCS	--	--	--	--	--	--	8	8	8
6	Sodium bi carbonate	10	20	30	10	20	30	10	20	30
7	MCCPH 101	48	48	48	48	48	48	48	48	48
8	Magnesium stearate	2	2	2	2	2	2	2	2	2
9	Aerosil	2	2	2	2	2	2	2	2	2

Table 3: Formulation chart (GRFT19 to GRF27)

S.No	Ingredients (mg)	GRFT19	GRFT20	GRFT21	GRFT22	GRFT23	GRFT24	GRFT25	GRFT26	GRFT27
1	Tramadol	100	100	100	100	100	100	100	100	100
2	HPMC K100M	30	30	30	30	30	30	30	30	30
3	Crosspovidone	8	8	8	--	--	--	--	--	--
4	SSG	--	--	--	8	8	8	--	--	--
5	CCS	--	--	--	--	--	--	8	8	8
6	Sodium bi carbonate	10	20	30	10	20	30	10	20	30
7	MCC PH 101	48	48	48	48	48	48	48	48	48
8	Magnesium stearate	2	2	2	2	2	2	2	2	2
9	Aerosil	2	2	2	2	2	2	2	2	2

floating drug delivery systems seems to be the promising delivery systems for control release of drugs.

MATERIALS AND METHODS

Materials

Tramadol Hcl, HPMC K4M, HPMC K15M and HPMC K100M were obtained from saushan pharmaceutics pvt. limted as gift sample. Other chemicals were obtained from DR.reddy's laboratory Hyderabad.

Preparation of Tramadol Hcl Floating tablets by wet granulation method

Tramadol Hcl Floating tablet containing tramadol HCl were prepared in different batch formulations in all batches drug is kept as 100mg with varing propotions of other ingredients by wet granulation technique using varying concentration of different grades of polymer with sodium bi carbonate. Polymer and tramodal HCl were mixed homogeneously using glass mortar and pestle. Isopropyl alcohol was used as granulating agent, granules were prepared by passing the wet coherent mass through # 16 sieve. The granules were dried in hot air oven at a temp of 45-55 ^{o}C. Dried granules were sieved through 20/44, mixed with sodium bi carbonate as gas generating agent and lubricated with magnesium stearate and aerosil just five minutes before compression. Lubricated granules were compressed in ERWEKA TR-40 rotary tablet machine. (Sanjay S Patel et al., 1996)

Table 4: Post compression parameters

Formulation code	Mean hardness (kg/cm^2)	Average weight (mg)	Mean content	Swelling index (%)	Floating lag (min)	Floating time (hrs)
GRFT1	4.21	203.2	97.63	15.15	3	8
GRFT4	4.27	203.7	96.71	13.3	50	8
GRFT7	4.51	206.8	98.23	40.14	2	8
GRF10	4.49	208.5	99.19	8.56	5	8
GRF13	4.77	201.4	94.78	22.33	3	8
GRF16	4.65	204.7	92.83	30.1	4	8
GRF19	4.46	206.3	95.49	35.83	7	8
GRF22	4.32	208.6	96.14	38.11	3	8
GRF25	4.10	205.6	97.13	45.23	2	Above 8

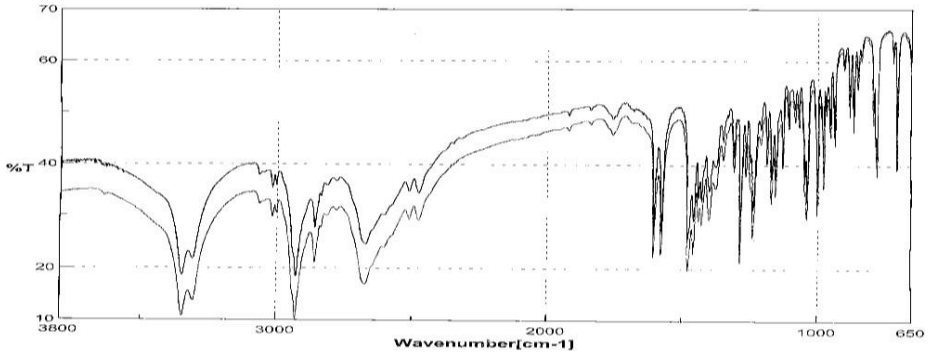

Figure 1: FTIR Spectrum of pure compound was compared with the standard Tramadol HCl

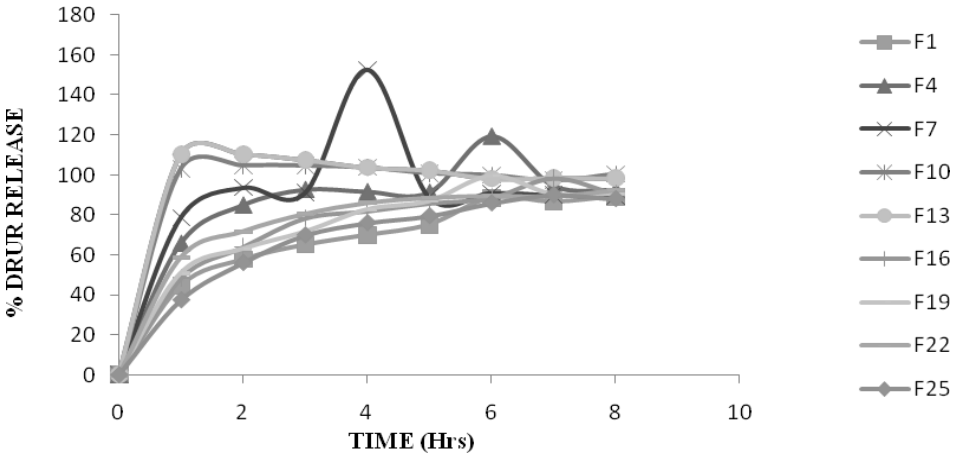

Figure 2: Dissolution Profile

Preformulation studies

Bulk density

The bulk density was obtained by dividing the mass of power by the bulk volume.The powder sample under the test was screened through sieve no.18 and the sample equivalent to 10gm was accurately weighed and filled in a100ml of graduated cylinder and the powder was tapped to the reduction in its volume to a standard level then the powder density was calculated.

$$D_b=M/V$$

Where, M=Weight in gms of powder; V=Final volume of the powder.

Angle of repose

It has been defined as the maximum angle possible between the surface pile of the powder to the horizontal plane. The angle of repose for the granules was determined by the funnel method. The granules were allowed to flow through funnel orifice on a graph sheet, the circle was made and height was measured.

$$Tan\theta=(h/r)$$

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

Compressibility index

An indirect method of measuring of powder flow from bulk densities was developed by carr.The percentage compressibility of the powder was direct measure of

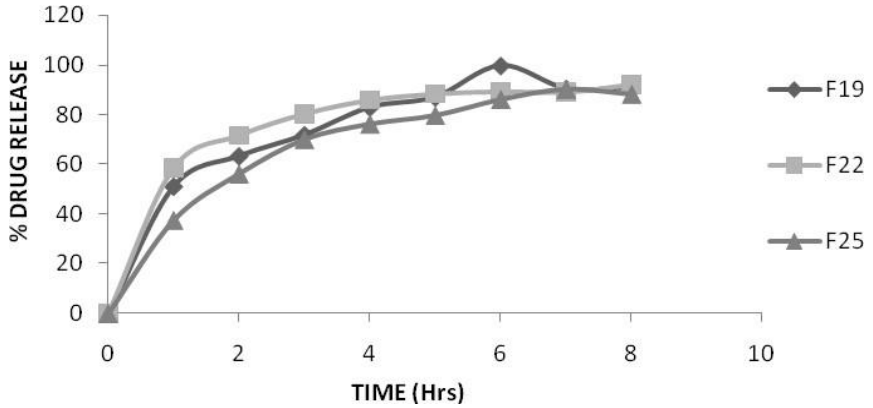

Figure 3: Dissolution Study of Optimized Formulation F19, F22, F25

the potential powder arch or bridge strength and stability.

$$\text{Carr's index}=(D_f-D_o)/D_{f\times100}$$

Where, D_f=Poured bulk density; D_o=Tapped or consolidated bulk density.

Hausner's Ratio

Tapped density and bulk density were measured for the powders and then hausner ratio was calculated by the following formula.(Ansel, Nicholas G.Poporich et al.,1999)

$$\text{Hausner's ratio}=D_o/D_f$$

Where, D_f =Bulk density; D_o=Tapped density

Post-compressional studies

Hardness and friability test

Hardness of tablet was tested using a monsantto hardness tester.Frability was determined by weighing 10 tablets after dusting, placing them in the Friabilator (Roche Friabilator) and rotating the plastic cylinder vertically at 25rpm for 4 min. After dusting, the total remaining weight of the tablets was recorded and the percent frability(PF) was calculated by using formula

PF=(Weight orginal-Weight final)/Weight original×100

Weight variation test

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation if not more than the two of the individual tablet weight deviate from the average weight by more than the percentage shown in the index.

***In-vitro* buoyancy studies**

In-vitro buoyancy studies were performed for all twenty five formulations as per the method described by rouge et al., 1998. The randomly selected tablets from each formulation were kept in a 100 ml beaker contains simulated gastric fluid, PH 1.2 as per USP. The time taken for the tablet to rise to surface of the medium was taken as floating lag time t. The duration of time the dosage form constantly remained on surface of medium was determined as total floating time.(Yuvarej Singh Tanwaret al., 2007)

Drug Content Estimation

Drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was determined and added in100ml of 0.1N HCL fallowed by stirring for 30mts. The solution was filtered, diluted suitably and the absorbance of resultant solution was measured spectrometrically at 270nm using 0.1 N HCL as blank.

Determination of swelling index

Swelling index of tablets was determined in 0.1N HCl at room temperature. The swollen weight of tablets was determined at pre defined time intervals over a period of 5h. The swelling index, and was calculated from fallowing equation

$$SI = \frac{weight\ of\ tablet\ at\ a\ time\ (t) - \ Initial\ weight\ of\ tablet}{Initial\ weight\ of\ tablet} \times 100$$

Figure 4: Swelling index of tablets before and after swelling

***In vitro* drug release study**

The releases of Tramodal HCl from different formulations were determined using United States pharmacopeia (USP) paddle apparatus2 under sink conditions. The dissolution medium was 900ml a 0.1N HCL solution (ph=1.2) , at 37+0.2^{O}C and the stirring speed was maintained 50 rpm of the A samples were withdrawn with every half an hour and one hour up to a period of 8 to 10 hrs. The sample were diluted suitably and filtered. The required dilutions were made with and the solution was analyzed for the drug content by using UV detector detecting at maximum wave length at 270 nm. From this percentage drug release was calculated and this was plotted against function of time to study the pattern of drug release. The *in vitro* drug release profile of tablet from each batch was constructed. The plot of cumulative percentage drug release versus time was plotted and depicted here in figure no: 2 & 3. (Moursy NM et al., 2003).

Drug release kinetics

To describe the kinetics of the drug release from tablet, mathematical models such as zero-order, first order, Higuchi and korsmeyer-peppas models were used. The criterion for selecting the most appropriate model was chosen on the basis of the goodness or fit test (Mukhopadhyayas et al., 2010).

Figure 5: Determination of floating time and floating lag time

RESULTS AND DISCUSSION

Tramadol Hcl Floating tablet containing tramadol HCl were prepared by wet granulation technique using varying concentration of different grades of polymer with sodium bi carbonate. Polymer and tramodal HCl were mixed homogeneously using glass mortar and pestle. Isopropyl alcohol was used as granulating agent, granules were prepared by passing the wet coherent mass through # 16 sieve. The granules were dried in hot air oven at a temp of 45-55^{0}c. Dried granules were sieved through 20/44#, mixed with sodium bi carbonate as gas generating agent and lubricated with magnesium stearate and aerosil just five minutes before compression. Lubricated granules were compressed in ERWEKA TR-40 rotary tablet machine. Thus prepared tablet were randomly subjected for in vitro release studies the results were interpreted for its kinetic pattern and compared with existing formulations. The result of these studies indicates that when hypromellose mixed with croscarmellose sodium which increase the gastric residence time is more , it is due to hydrophilic nature of HPMC which trap water and it increase in size and become gel. When the gel combined with carmellose sodium it retards the release of tramodal HCl being this formulation with effervescent nature and adhering property it slowly release the medicament from the dosage form.

CONCLUSION

The result of these studies indicates that when hypromellose mixed with croscarmellose sodium which increase the gastric residence time is more, it is due to hydrophilic nature of HPMC which trap water and it increase in size and become gel. When the gel combined with carmellose sodium it retards the release of tramodal HCl being this formulation with effervescent nature and adhering property it slowly release the medicament from the dosage form. Floating drug delivery desing with Tramadol hydrochloride with the varying grades of hypermellose and it is subjected for various studies as per literature like FTIR and other pre-compression and post compression studies. It reveals that with hypermellose K100 M with super disintegrant cross-carmellose sodium shows extended release by residing at GIT for long time and there were no interaction with any excipient. The present investigation towards buoyant delivery system was found to be satisfactory. Further *in-vivo* studies can be carried out to confirm the actual mode of release of the candidate in the stomach.

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