Development and evaluation of controlled release mucoadhesive tablets of Tramadol Hydrochloride

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ABSTRACT

The present investigation concerns the development of mucoadhesive tablets of Tramadol Hydrochloride which were designed to prolong the gastric residence time after oral administration. Tablets of Tramadol Hydrochloride were formulated using four mucoadhesive polymers namely guar gum, xanthan gum, HPMC K15M and HPMC K100M and carried out studies for its evaluation parameters. Formulations F15 and F16 containing polymers of Xanthan gum, HPMC K100M and HPMC K15M were established to be the optimum formulation since it shows optimum bioadhesive force, swelling index & desired evaluation standards. Further investigations are needed to confirm the in vivo efficiency, long term stability studies are needed to stabilize the controlled released formulations

Key-words: Mucoadhesive tablets, Tramadol Hydrochloride, Formulation, Evaluation

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INTRODUCTION

Extensive efforts have been focused on targeting a drug or drug delivery system in a particular region of the body for extended period of time, not only for local targeting of drug but also for better compliance of systemic drug delivery. The concept of mucosal adhesive or mucoadhesive was introduced into the controlled drug delivery area, in the early 1980. Mucoadhesive are synthetic or natural polymer, which interact with the mucus layer covering the mucosal epithelial surface, and mucin molecules constituting a major part of mucus. The concept of mucoadhesive as alters many investigator to the possibility that this polymer can be used over come physiological barrier in long-term drug delivery. They render the treatment more effective and safe, not only for topical disorder but also for systemic problems.[1-2]

Tramadol is not a nonsteroidal antiinflammatory drug (NSAID), and does not have the increased risk of stomach ulceration and internal bleeding that can occur with the use of NSAIDs. Tramadol and its O-desmethyl metabolite (M1) are selective, weak OP3-receptor agonists. Opiate receptors are coupled with G-protein receptors and function as both positive and negative regulators of synaptic transmission via G-proteins that activate effector proteins. As the effector system is adenylate cyclase and cAMP located at the inner surface of the plasma membrane, opioids decrease intracellular cAMP by inhibiting adenylate cyclase. Subsequently, the release of nociceptive neurotransmitters such as substance P, GABA, dopamine, acetylcholine and noradrenaline is inhibited. The analgesic properties of Tramadol can be attributed to norepinephrine and serotonin reuptake blockade in the CNS, which inhibits pain transmission in the spinal cord. The (+) enantiomer has higher affinity for the OP3 receptor and preferentially inhibits serotonin uptake and enhances serotonin release. The (-) enantiomer preferentially inhibits norepinephrine reuptake by stimulating alpha(2)-adrenergic receptors.

Tramadol is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of a 100 mg oral dose is 75%. Administration with food does not significantly affects its rate or extent of absorption; therefore, it can be administered without regard to the meals. Steady state is achieved after two days of a 100mg four times daily dosing regimen of Tramadol. The plasma half life of the tramadol was 5 - 7 hours. Binding to human plasma proteins is ~ 20%. [3-4]

METHOLODOGY

During the course of present investigation following methodology were adopted.

1. Physical parameters of Drug and Polymers[5]

- **Bulk density**

  Bulk density is defined as a mass of a powder divided by the bulk volume.

  A sample powder of Tramadol Hydrochloride (5 g) was introduced in 100 ml graduated cylinder. The volume of the material was noted on graduated cylinder. The bulk density was calculated by the formula given below;

  $$\text{Bulk density } (\rho_0) = M/Vo$$

  Where, M = mass of the powder
  Vo = volume of the powder

- **Tapped Density**
  The powder sample under test was screened through sieve no. 18 and the weight of sample equivalent to 5 g was filled in 100 ml graduated cylinder. The mechanical tapping of the cylinder was carried out using at a nominal rate of 300 drops per minute for 500 times initially and the tapped volume V_o was noted. Tapping was proceeding further for an additional tapping 750 times and tapped volume, V_b was noted. The difference between two tapping volume was less than 2%, so V_b was considered as a tapped volume V_f. The tapped density was calculated in g/ cm^3 by the formula,

  $$\text{Tapped density } (\rho_t) = M/V_f$$

  Where, M = weight of sample powder taken
  V_f = tapped volume

- **Compressibility Index**
  The bulk density and tapped density was measured and compressibility index was calculated by using the formula,

  $$C.I. = \{(\rho_t - \rho_o)/ \rho_t\} \times 100$$

  Where, ρ_t = tapped density
  ρ_o = bulk density

- **Hausner ratio**
  Tapped density and bulk density were determined and the Hausner ratio was calculated by using the formula,

  $$\text{Hausner ratio} = \rho_t/\rho_o$$

  Where, ρ_t = tapped density
  ρ_o = bulk density

2. Formulation of mucoadhesive tablet[6]

Mucoadhesive matrix tablets containing Tramadol Hydrochloride were prepared by wet granulation technique using variable concentrations of HPMC K15M, HPMC K100M, Xanthan gum, Guar gum. All the ingredients except Avicel PH 102, magnesium stearate and talc were blended in glass mortar uniformly. All the ingredients were mixed and passed through sieve no 60. Granulation was done with sufficient binding solution of PVP K30 and isopropyl alcohol. Wet mass was passed through sieve no 12 and dried at 45-55^{o}c for 2 hrs. Dried granules were sized by sieve no. 18 and mixed with Avicel PH 102, magnesium stearate and talc. Granules obtained were compressed with 9mm punch. The weight of the tablets was kept constant for formulations F1 to F16.

3. Evaluation of mucoadhesive tablets[7-8]

All the prepared mucoadhesive tablets were evaluated for following parameters.

- **Hardness**

  Hardness was measured using Monsanto hardness tester. For each batch three tablets were tested.

- **Friability**

  Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dusted and weighed again. The percentage friability was measured using the formula,

  $$\% F = \{1-(W_o/W)\} \times 100$$

  Where, % F = friability in percentage
  W_o = Initial weight of tablet
  W = weight of tablets after revolution

- **Weight Variation**

  Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more then two of the individual tablet weight deviate from the average weight by more than the percentage shown in Table and none deviate by more than twice the percentage shown.

Percentage deviation allowed under weight variation test

Average weight of tablet (mg)	Percentage deviation
130 or less	10
130-324	7.5
More than 324	5

- **Thickness**

  Three tablets were selected randomly from each batch and thickness was measured by using vernier caliper.

- **Drug content**

  Three tablets from each batch were weighed accurately and powdered powder equivalent to 100 mg Tramadol Hydrochloride was shaken with 100ml of 0.1 N Hydrochloric acid in 100ml volumetric flask and from this 5 ml was pipetted out and than dilute upto 100 ml. From standard solution again 5 ml pipetted out and diluted up to 100 ml in 100 ml volumetric flask. Resulting solution was filtered and assayed at 271 nm and content of Tramadol Hydrochloride was calculated.

- **Swelling index**

  Swelling of tablet excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule, breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of % weight gain by the tablet. For each formulation

batch, one tablet was weighed and placed in a beaker containing 200 ml of buffer media. After each interval the tablet was removed from beaker and weighed again up to 8 hours. The swelling index was calculated using following formula.

$$\text{Swelling Index (S.I.)} = (Wt-Wo)/Wo$$

Where, S.I. = Swelling index
W_t = Weight of tablet at time t
W_o = Weight of tablet before placing in the beaker

RESULTS

Tramadol Hydrochloride is a centrally acting synthetic opioid analgesic and is often used to treat moderate and severe pain. The plasma half life of the Tramadol Hydrochloride was 5 - 7 hours, so it is desirable to formulate the controlled release formulation which would increase the bioavailability and suitable for twice daily medication, it was desirable to deliver such drug in a gastro retentive dosage form or mucoadhesive drug delivery systems which would prolong the gastric residence time of drug thereby giving sufficient time for drug delivery system to release the drug and efficient absorption of active moiety. It was suggested that mucoadhesive drug delivery system are easiest approach for technical and logical point of view among the gastro retentive drug delivery system, so, for the present study mucoadhesive drug delivery system was chosen.

In the present investigation, an attempt was made to deliver Tramadol Hydrochloride via oral mucoadhesive drug delivery system to the vicinity of absorption site by prolonging the gastric residence time of the dosage form. For the formulation of oral mucoadhesive tablet various polymer used like Hydroxypropyl methylcellulose K15 M, K 100 M, Xanthan gum and Guar gum, used as hydrophilic matrix forming and mucoadhesive polymer in varying concentration along with Magnesium stearate, talc and Avicel PH 102 as filler.

Various physical parameters of both the drug and polymers were studied (Table 1 & 2). Tablets were carried out to various evaluation parameters such as drug content, hardness, weight variation, friability and swelling index (Table 3 & 4). It was revealed that the tablets of all formulations had acceptable physical parameters. Tablets of formulations F15 and F16 had good mucoadhesion along with good swelling behaviors.

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Table 1. Physical parameters of Tramadol Hydrochloride (Drug)

Bulk density (gm/cm^3)	Tapped Density (gm/cm^3)	Compressibility Index	Hausner Ratio
0.241	0.335	28.059	1.390

Table 2. Physical parameters of polymers

Polymers	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Compressibility Index	Hausner Ratio
HPMC K15M	0.312	0.523	40.34	1.60
HPMC K100M	0.600	0.770	22.08	1.28
Xanthan gum	0.572	0.478	0.523	2.57
Guar gum	0.363	0.572	36.40	1.41

Table 3.Physical Properties of Tablets of Batch F1 to F16

Batch no.	Weight Variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Drug content uniformity (mg)
F1	240.7±5.02	6.7±0.252	3.03±0.11	0.55	98.94
F2	240.5±4.00	6.6±0.289	2.80±0.05	0.58	99.10
F3	239.6±3.99	6.4±0.462	2.76±0.05	0.53	98.92
F4	239.4±3.77	7.1±0.361	2.70±0.15	0.39	98.72
F5	240.3±3.01	6.6±0.173	2.66±0.05	0.41	98.19
F6	240.3±2.72	7.4±0.551	2.93±0.15	0.48	98.92
F7	240.1±2.17	6.4±0.436	2.55±0.08	0.61	97.10
F8	240.2±2.29	6.9±0.306	2.62±0.05	0.72	99.28
F9	239.8±2.05	7.1±0.458	2.53±0.052	0.67	98.30
F10	240.1±2.47	6.6±0.173	2.81±0.076	0.48	97.46
F11	240.0±2.11	6.6±0.208	2.76±0.115	0.39	98.19
F12	241.0±2.55	6.7±0.208	2.83±0..064	0.47	98.82
F13	240.1±2.13	6.7±0.666	2.53±0.052	0.54	97.30
F14	241.1±2.57	6.4±0.603	2.81±0.076	0.56	97.46
F15	240.5±2.23	7.1±0.208	2.76±0.115	0.44	99.19
F16	240.3±2.25	7.0±0.200	2.83±0..064	0.38	99.82

Each reading is an average of three determinations (Avg.± S.D)

Table 4. Swelling Index of Tablets of Batch F1 to F16

Batch no.	Time (hrs)								
	0	1	2	3	4	5	6	7	8
F1	0	0.522	0.582	0.642	0.686	0.920	1.028	--	--
F2	0	0.544	0.588	0.652	0.692	0.980	1.035	--	--
F3	0	0.566	0.589	0.672	0.810	0.980	1.076	1.092	--
F4	0	0.599	0.724	1.116	1.241	1.324	1.344	1.086	--
F5	0	0.610	0.689	0.710	0.852	0.934	1.040	1.081	1.101
F6	0	0.625	0.694	0.740	0.763	0.857	0.983	1.091	1.110
F7	0	0.633	0.700	0.748	0.810	0.915	1.000	1.099	1.121
F8	0	0.670	0.720	0.760	0.840	0.910	1.005	1.126	1.139
F9	0	0.690	0.810	1.110	1.138	1.144	1.150	1.156	1.169
F10	0	0.599	0.710	0.790	0.810	1.026	1.132	1.141	1.149
F11	0	0.620	0.803	0.926	1.110	1.030	1.041	1.048	1.052
F12	0	0.630	0.899	0.910	1.118	1.138	1.146	1.151	1.154
F13	0	0.526	0.822	1.045	1.142	1.198	1.224	1.236	1.242
F14	0	0.656	0.942	1.124	1.145	1.185	1.215	1.266	1.275
F15	0	0.729	0.926	1.026	1.089	1.156	1.210	1.410	1.626
F16	0	0.700	0.892	1.018	1.076	1.125	1.200	1.400	1.589

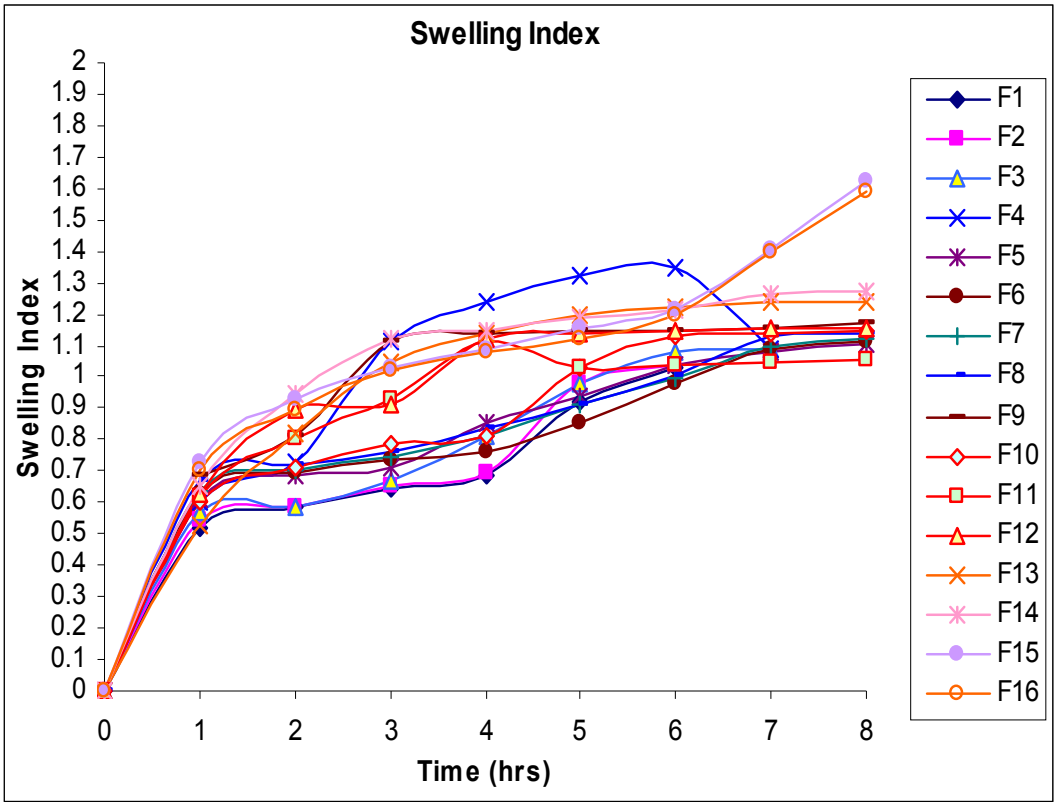

Fig. 1:- Graph of the Swelling index versus Time (hr).

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