Original Article

Microspheres of tramadol hydrochloride compressed along with a loading dose: A modified approach for sustaining release

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ABSTRACT: The purpose of this research was to study mucoadhesive microspheres of tramadol hydrochloride compressed into tablet along with a loading dose. Microspheres containing tramadol hydrochloride were prepared by employing sodium alginate in combination with a mucoadhesive polymer, *i.e.*, Carbopol 971P. An orifice-ionic gelation method was used to prepare the microspheres. A 3^2 factorial design was used to investigate the combined effect of two independent formulation variables in the preparation of microspheres. The concentration of sodium alginate (X_1) and Carbopol 971P (X_2) were selected as independent variables. Nine batches were used in the experimental design and evaluated for swelling index, mucoadhesion, and drug entrapment efficiency. A surface plot is presented to graphically represent the effect of the independent variables on the evaluation parameters. The best batch exhibited drug entrapment efficiency of 70.12%, swelling index of 2.3 and mucoadhesion of 95.42%. Microspheres showing maximum drug entrapment were compressed with the loading dose and subjected to *in vitro* dissolution studies. Drug release from tablets was found to follow a matrix model. Initial burst release from these tablets indicated the release of the loading dose and then a sustained effect over the time. This modified approach to formulation of tablets was found to be effective in sustaining drug release.

Keywords: Carbopol 971P, factorial design, mucoadhesive microspheres, tramadol hydrochloride

1. Introduction

A sustained release dosage form is mainly designed for maintaining therapeutic blood or tissue levels of the drug for an extended period of time with minimized local or systemic adverse effects. Economy and greater patient compliance are other advantages (*1*). In recent years, clinical studies on tramadol hydrochloride have demonstrated that this drug is an effective agent for moderate to severe chronic pain (*2-5*). The half-life of the drug is about 5.5 h and the usual oral dosage regimen is 50 to 100 mg every 4 to 6 h with a maximum dosage of 400 mg/day (*6*). To reduce frequent administration of dosage form and to improve patient compliance, a sustained-release formulation of tramadol is desirable. The drug is freely water soluble and hence judicious selection of release retarding excipients is necessary to achieve a constant *in vivo* input rate of the drug. Various approaches have been used by researchers to sustain drug release in the form of tablets (*7-9*).

Microsphere carrier systems made from naturally occurring biodegradable polymers have attracted considerable attention for several years in sustained drug delivery. Microspheres form an important part of novel drug delivery systems (*10-12*). They have varied applications and are prepared using various polymers. However, the success of these microspheres is limited due to their short residence time at the site of absorption. It would, therefore, be advantageous to have a means for providing an intimate contact of the drug delivery system with the absorbing membranes (*13-17*). This can be achieved by coupling mucoadhesion characteristics to microspheres and developing mucoadhesive microspheres. Mucoadhesive microspheres have advantages including: efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site (*18-21*).

A modified approach of compressing the mucoadhesive microspheres into tablets with loading dose will provide efficient delivery by causing burst release of tablet with loading dose into the stomach and then attachment of mucoadhesive microspheres to gastric mucosa will provide sustained release of the drug.

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2. Materials and Methods

2.1. *Materials*

Tramadol was a gift from Panacea Biotec (New Delhi, India). Avicel PH-102 was a gift from Okasa Pharmaceuticals (Maharashtra, India), Carbopol 971P was supplied by Noveon Asia Pacific Ltd. (Hong Kong, China), Sodium starch glycolate was a gifted from Okasa Pharmaceuticals (India). Sodium alginate was purchased from Merck India (Mumbai, India). All other reagents and chemicals were of analytical grade.

2.2. *Preparation of microspheres*

Batches of microspheres were developed using a 3^2 factorial design (*22,23*). The advantages of a factorial design include greater precision. By using a factorial design, it is possible to examine the effect of one variable when other factors are changed, which is not possible using traditional methods of investigation. The independent formulation variables were taken at three different levels: low, medium and high (-1, 0, and 1, respectively; Table 1). The factors selected were X_1 – weight of sodium alginate and X_2 – weight of Carbopol 971P. The Orifice-Ionic Gelation Method was used for preparation of microspheres as follows:

Sodium alginate and Carbopol 971P were dispersed in purified water (50 mL) to form a homogeneous polymer mixture (Table 2). Tramadol (1,000 mg) was added to the polymer premix and mixed thoroughly to form a smooth viscous dispersion. The resulting dispersion was then sprayed through a glass nozzle with a 1.61 mm inner diameter and 4 mm outer diameter into calcium chloride (10%, w/v) solution. The addition was done with continuous stirring. Produced droplets were retained in the calcium chloride solution for 15 min to complete the curing reaction and to produce rigid spherical microspheres. The resulting microspheres were collected using decantation, and the separated product was washed repeatedly with purified water to remove excess calcium impurities deposited on the surface of microspheres and then dried at 45°C for 12 h.

Table 1. Coded levels and their translation into actual units

Coded level	Variables	
	X_1 (weight of sodium alginate) (mg)	X_2 (weight of carbopol 971P) (mg)
–1	500	500
0	750	750
+1	1,000	1,000

2.3. *Characterization and evaluation of microspheres*

2.3.1. *Surface characterization, particle size and swelling index of microspheres*

Prepared microspheres were morphologically characterized. The particle size of the microspheres was determined using optical microscopy. Approximately 100 microspheres were counted for particle size using a calibrated optical microscope (Labomed CX RIII, Ambala, India). For estimating the swelling index, the microspheres (~100) were suspended in 5 mL simulated gastric fluid USP (pH 1.2). The particle size was monitored by microscopy every 1 h using an optical microscope (Labomed CX RIII). The increase in particle size of the microspheres was noted for up to 8 h and the swelling index was calculated as described by Ibrahim (*24*).

Swelling index = Volume after 12 h / Original volume ----- (1)

2.3.2. *In vitro mucoadhesion evaluations*

The mucoadhesive force of all the batches was determined by the method of Choi, *et al*. (*25*). A section of gastric mucosa was cut from sheep's stomach and instantly attached with mucosal side out onto each glass vial using a rubber band. The vials with mucosa were stored at 37°C for 5 min. The next vial with a section of mucosa was connected to the balance in inverted position while the first vial was placed on a height adjustable pan. A fixed weight of mucoadhesive microspheres was placed onto the gastric mucosa of the first vial. Then the height of the second vial was adjusted so that the mucosal surfaces of both vials came in intimate contact. Ten minutes of contact was used. The weight was increased in the pan until vials were detached. Mucoadhesive force

Table 2. Formulation design of mucoadhesive microspheres

Batch No.	X_1	X_2	Sodium alginate (mg)	Carbopol 971P (mg)	Tramadol HCl (mg)
F1	–1	–1	500	500	1,000
F2	0	–1	750	500	1,000
F3	1	–1	1,000	500	1,000
F4	–1	0	500	750	1,000
F5	0	0	750	750	1,000
F6	1	0	1,000	750	1,000
F7	–1	1	500	1,000	1,000
F8	0	1	750	1,000	1,000
F9	1	1	1,000	1,000	1,000

Table 3. Results of various evaluation parameters of mucoadhesive microspheres

Batch No.	Swelling index	Percentage mucoadhesion	Drug entrapment efficiency (%)
F1	1.4	82.34	61.83
F2	1.78	86.23	63.23
F3	2.1	89.54	65.42
F4	1.68	86.65	62.56
F5	1.97	88.64	65.45
F6	2.1	90.12	66.21
F7	1.87	87.31	64.32
F8	2.1	92.12	67.41
F9	2.3	95.42	70.12

was the minimum weight required to detach two vials. The mucosa was changed for each measurement.

% Mucoadhesion = {(Wt. of sample – Wt. of detached particles)/ Wt. of sample} × 100 ----- (2)

2.3.3. *Drug entrapment efficiency*

Microspheres (50 mg) were crushed in a glass mortar-pestle and the powdered microspheres were suspended in 10 mL phosphate buffer (pH 7.4). After 24 h, the solution was filtered and the filtrate was analyzed for drug content. The drug entrapment efficiency was calculated using the following formula.

Microencapsulation efficiency = Practical drug content / Theoretical drug content × 100 ----- (3)

2.3.4. *Compression of microspheres with loading dose*

The batch showing the maximum percentage of entrapment was considered for preparation of tablet. The microspheres equivalent to 100 mg were accurately weighed and compressed with 50 mg of tramadol as loading dose with 200 mg of Avicel PH-102 and sodium starch glycolate (7% of the total weight of mix) using a single punch tablet compression machine.

2.3.5. *In vitro dissolution studies*

Tablets made up by compressing microspheres showing greater entrapment efficiency are studied for dissolution testing with USP II apparatus at 50 rpm and at temperature 37 ± 1°C. Samples were withdrawn at different time intervals and were assayed at 271.5 nm for tramadol content using Shimadzu UV-Vis Spectrophotometer (UV 1700; Shimadzu Corporation, Kyoto, Japan).

3. Results

3.1. *Surface characterization, particle size and swelling studies*

Mucoadhesive microspheres of tramadol prepared were well-rounded spheres with ridges of shrinkage due to presence of Carbopol 971P coat. Particle size was in between range of 217 µm to 368 µm. The swelling index (Table 3) varied from 1.4 to 2.3 (Figure 1) and showed correlation coefficient of 0.9488.

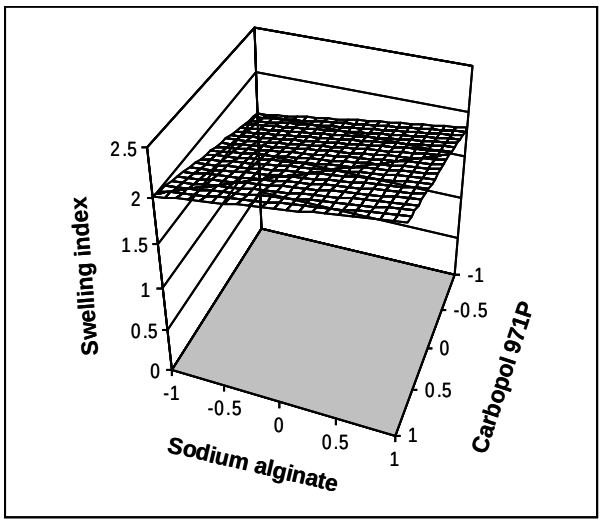

Figure 1. Surface response showing effect of variables on swelling index.

3.2. *In vitro mucoadhesion evaluation*

The percentage mucoadhesion varied from 82.34 to 95.42% (Table 3; Figure 2) and showed good correlation coefficient (0.9543).

3.3. *Drug entrapment efficiency*

Drug entrapment efficiency was found to be 61.83% to 70.12% (Table 3). It was found that increasing Carbopol 971P concentration was found to increase in entrapment efficiency. Correlation coefficient was found to be 0.9377. The surface response showing effect of variables on drug entrapment efficiency is shown in Figure 3.

3.4. *In vitro dissolution studies*

Comparative analysis of dissolution profiles (Figure

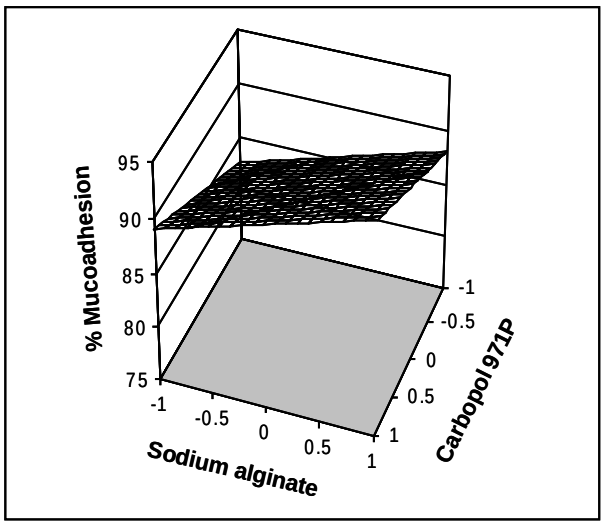

Figure 2. Surface response showing effect of variables on percentage mucoadhesion.

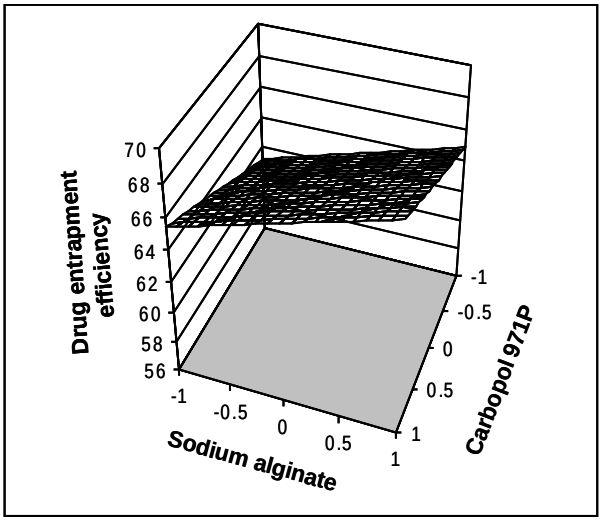

Figure 3. Surface response showing effect of variables on drug entrapment efficiency.

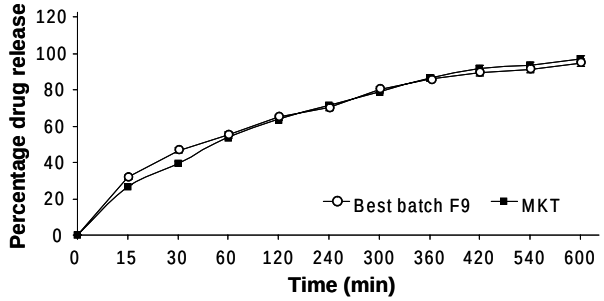

Figure 4. *In vitro* dissolution profile of best batch F9 and marketed formulation (MKT).

4) between compressed tablets with loading dose and marketed sustained release tablets showed initial burst release in case of prepared formulation which is 31.922 ± 1.12. This release is equivalent to 47.88 mg. The f_2 value (Similarity factor) was found to be 66.12. The Korsmeyer-Peppas release exponent of prepared formulation was found to be 0.2701.

4. Discussion

4.1. *Surface characterization, particle size and swelling studies*

The drug-loaded microspheres were spherical and yellowish white in appearance and whiteness gradually increases with increase in Carbopol 971P concentration. Microspheres with a coat of mucoadhesive polymer were found to be discrete, spherical, free flowing and of monolithic matrix type. The microspheres were uniform in size for each batch. Micromeritic property such as particle size is mainly governed by the polymer concentration. Particle size increases with increasing Carbopol 971P concentration. This may be due to increased viscosity of the dispersion, which affects the performance of spraying the mixture, causing formation of larger droplets.

The amount of polymer directly affected the solvent transfer rate and thus as the Carbopol 971P concentration increases the swelling index also increases. This may be due to higher water sorption capacity of Carbopol 971P than sodium alginate. Good correlation coefficient of 0.9488 indicates that amount of Carbopol 971P and sodium alginate directly affects the swelling index.

4.2. *In vitro mucoadhesion evaluation*

The percentage mucoadhesion varied from 82.34 to 95.42% (Table 3) and showed a good correlation coefficient (0.9543). At higher concentrations of both variables mucoadhesion increased, this may be attributed to an increase in particle size that causes an increase in mucoadhesion. Thus we can conclude that the amount of Carbopol 971P and sodium alginate directly affects the percentage of mucoadhesion.

4.3. *Drug entrapment efficiency*

The drug entrapment efficiency is an important variable for assessing the drug loading capacity of microspheres and their drug release profiles, thus suggesting the amount of drug availability at the site. These parameters are dependent on the process of preparation, physicochemical properties of drug and formulation variables. Batch F9 (70.12%) which showed maximum percentage entrapment was considered for preparation of tablet.

4.4. *In vitro dissolution studies*

Dissolution testing is a critical parameter for pharmaceutical dosage forms (*26*). Initial burst release in

the case of prepared formulation is equivalent to 47.88 mg. This indicates that prepared formulation releases the loading dose at 15 min. Subsequent release occurs from microspheres representing sustained release. The dissolution profile of marketed formulation follows a Matrix model. The model independent method such as similarity factor (f_2) provides a simple way to compare dissolution data. US FDA guidance proposes that f_2 values of 50-100 indicate equivalence in dissolution profiles. The f_2 value was found to be 66.12 indicating similarity in dissolution profiles. The Korsmeyer – Peppas release exponent of prepared formulation indicates non-Fickian diffusion, *i.e.*, initially there is rapid release, which is followed by tailing off over time.

5. Conclusion

The results of a 3^2 full factorial design revealed that the concentration of Carbopol 971P and sodium alginate significantly affected the dependent variables percentage mucoadhesion, swelling index, and drug entrapment efficiency. The mucoadhesive microspheres exhibited good mucoadhesive properties in an *in vitro* test. The entrapment efficiency increased as the concentration of Carbopol 971P increased. The microsphere batch showing maximum entrapment was compressed into tablets which showed an initial burst release of loading dose. This novel approach indicates a sustained release tablet with a loading dose can be helpful to achieve an immediate therapeutic level followed by sustained release over time.

References

1. George M, Grass IV, Robinson JR. Sustained and controlled release delivery systems, Marcel Dekker, New York, USA, 1978; pp. 124-127.
2. Osipova NA, Novikov GA, Beresnev VA, *et al*. Analgesic effect of tramadol in cancer patients with chronic pain: a comparison with prolong the action of morphine sulfate. Curr Ther Res Clin Exp. 1991; 50:812-821.
3. Sunshine A, Olson NZ, Zighelboim I, DeCastro A, Minn FL. Analgesic oral efficacy of tramadol hydrochloride in postoperative pain. Clin Pharmacol Ther. 1992; 51:740-746.
4. Lee CR, McTavish D, Sorkin EM. Tramadol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. Drugs. 1993; 46:313-340.
5. OrthoMcNeil Pharmaceutical. Ultram® (tramadol hydrochloride) tablets prescribing information. Raritan, New Jersey; 2001.
6. Scott LJ, Perry CM. Tramadol: a review of its use in perioperative pain. Drugs. 2000; 60:139-176.
7. Khullar P, Khar RK, Agarwal SP. Evaluation of guar gum in the preparation of sustained release matrix tablets. Drug Dev Ind Pharm. 1988; 24:1095-1099.
8. Mishra B, Seena J, Singh S, Sankar C. Development and characterization of matrix tablets of ketorolac tromethamine. Indian Pharm. 2003; 2:86-89.
9. Rani M, Mishra B. Effect of admixed polymers on diclofenac sodium release from matrix tablets. Pharm Pharmacol Lett. 2001; 2:76-78.
10. Woo BH, Jiang G, Jo YW, DeLuca PP. Preparation and characterization of a composite PLGA and poly (acryloyl hydroxymethyl starch) microsphere system for protein delivery. Pharm Res. 2006; 18:1600-1606.
11. Capan Y, Jiang G, Giovagnoli S, DeLuca PP. Preparation and characterization of poly (D,L-lactide-co-glycolide) microsphere for controlled release of human growth hormone. AAPS PharmSciTech. 2003; 4:E28.
12. Gohel MC, Amin AF. Formulation optimization of controlled release diclofenac sodium microspheres using factorial design. J Controlled Release. 1998; 51:115-122.
13. Vasir JK, Tambwekar K, Garg S. Bioadhesive microspheres as a controlled drug delivery system. Int J Pharm. 2003; 255:13-32.
14. Nagai T, Nishimoto Y, Nambu N, Suzuki Y, Sekine K. Powder dosage forms of insulin for nasal administration. J Controlled Release. 1984; 1:15-22.
15. Ikeda K, Murata K, Kobayashi M, Noda K. Enhancement of bioavailability of dopamine *via* nasal route in beagle dogs. Chem Pharm Bull. 1992; 40:2155-2158.
16. Illum L, Furraj NF, Critcheley H, Davis SS. Nasal administration of gentamycin using a novel microsphere delivery system. Int J Pharm. 1988; 46:261-265.
17. Schaefer MJ, Singh J. Effect of isopropyl myristic acid ester on the physical characteristics and *in vitro* release of etoposide from PLGA microspheres. AAPS PharmSciTech. 2000; 1:32.
18. Rao SB, Sharma CP. Use of chitosan as biomaterial: studies on its safety and hemostatic potential. J Biomed Mater Res. 1997; 34:21-28.
19. Lehr CM, Bouwstra JA, Schacht EH, Junginger HE. *In vitro* evaluation of mucoadhesive properties of chitosan and some other natural polymers. Int J Pharm. 1997; 78:43-48.
20. Henriksen L, Green KL, Smart JD, Smistad G, Karlsen J. Bioadhesion of hydrated chitosans: An *in vitro* and *in vivo* study. Int J Pharm. 1996; 145:231-240.
21. Chowdary KPR, Balatripura G. Design and *in vitro* evaluation of mucoadhesive controlled release oral tablets of glipizide. Ind J Pharm Sci. 2003; 55:591-594.
22. Bolton S. Pharmaceutical Statistics. Second ed. Marcel Decker, New York, USA, 1990; pp. 234.
23. Franz RM, Browne JE, Lewis AE. Experiment design, modeling and optimization strategies for product and process development. In: Libermann HA, Reiger MM, Banker GS, eds. Pharmaceutical Dosage Forms: Disperse Systems. Marcel Dekker, New York, USA, 1988; 1:427-519.
24. El-Gibaly I. Development and *in vitro* evaluation of novel floating chitosan microcapsules for oral use: comparison with non-floating chitosan microspheres. Int J Pharm. 2002; 249:7-21.
25. Choi HG, Jung JH, Ryu JM, Yoon SJ, Oh YK, Kim CK. Development of *in situ* gelling and mucoadhesive acetaminophen liquid suppository. Int J Pharm. 1998, 165:33-44.
26. Hosmani AH, Karmarkar AB, Karmarkar BB. Dissolution testing: past, current, and future perspectives. Current Pharma Research Journal. 2006; 1:1-10.

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