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Research Article

FORMULATION AND EVALUATION OF SUSTAINED RELEASE PELLETS OF TRAMADOL HYDROCHLORIDE

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ABSTRACT

The aim of the present research is to develop and evaluate a better sustained release multiple unit pellets (MUP) formulation of Tramadol hydrochloride. Dissolution and diffusion controlled systems have classically been of primary importance in oral delivery of medication because of their relative ease of production and cost compared with other methods of sustained or controlled delivery. Most of these systems are solids, although a few liquids and suspension have been recently introduced. The present work aimed at developing SR pellets of Tramadol HCl by Wurster process. FTIR studies showed no unacceptable extra peaks which confirm the absence of chemical interaction between the drug and polymer. Angle of repose, tapped density, bulk density values for the formulations were within the range which indicates that pellets prepared by Wurster process were satisfactory for further studies. The percentage drug content of Tramadol was determined by extraction with methanol and analyzed by using UV-visible spectrophotometer at 271nm.

KEYWORDS: Tramadol, Pellets, Wurster process.

INTRODUCTION

The goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period of time. This is generally accomplished by attempting "zero-order" release from the dosage form. Zero-order release constitutes drug release from the dosage form which is independent of the amount of drug in the delivery system (i.e. a constant release rate). Sustained-release systems generally do not attain this type of release and usually try to mimic zero-order release by providing drug in a slow first-order fashion (i.e., concentration release dependent). Systems that are designated as prolonged release can also be considered as attempts at achieving sustained-release delivery.

The term "Controlled- release drug product"[1] has been used to describe various types of oral extended release rate dosage forms, including sustained release (sustained action), prolonged release (long action) and retarded release.

A modified- release dosage form is defined "as one for which the drug release characteristics of time course and location are chosen to accomplish therapeutic convenience.

Principle behind SR/CR drug release

Dissolution and diffusion controlled systems have classically been of primary importance in oral delivery of medication because of their relative ease of production and cost compared with other methods of sustained or controlled delivery. Most of these systems are solids, although a few liquids and suspension have been recently introduced[1,2].

FACTORS INFLUENCING THE SELECTION OF A DRUG FOR ER/SR PRODUCTS

A.PHYSIOCHEMICAL PROPERTIES

1. Dose size: In general, a single dose of 0.5 - 11.0 gm for conventional dosage form is considered maximal dose size.

2. Aqueous Solubility: Extremes in aqueous solubility are under desirable in the preparation of a SR product. For drug with low water solubility, it will be difficult to incorporate into a SR formulation. The lower limit of solubility for such product has been reported to be 0.1 mg/ml.

3. Partition Co-efficient: Drug that are very lipid soluble or water soluble i.e. extremes in partition co-efficient, will demonstrate either low flux in to the tissues or rapid flux followed by accumulation in the tissues. Both extremes are undesirable for a SR system

4. Drug Stability: since most oral SR systems, by necessity are designed to release their contents over much of the length of the GIT, drugs which are unstable in the environment of the intestine might be difficult to formulate into prolonged release systems[3,4].

Eg: propanthdine and probanthine.

B. BIOLOGICAL PROPERTIES

- **Absorption:** Drugs that are slowly absorbed or absorbed with variable absorption rate are poor candidates for SR systems. For oral dosage forms the lower limit on the absorption rate constant is in the range of 0.17 to 0.23 hr^{-1} **(assuming GI transit time of 8-12 hr^{-1}).**
- **Metabolism:** Drugs that are significantly metabolized, especially in region of small intestine, can show decreased bioavailability from SR dosage forms, because fewer drugs is presented to enzymatic process during a specific period.
- **Therapeutic Index:** Drugs with a narrow therapeutic range which require precise control over the blood levels of the drug are unsuitable for SR dosage forms.
- **Half Life:** Drugs with a very short half life (>2 hr) require large amounts of drug to maintain sustained effects and drugs with longer life (<8hrs) because their effects are already sustained[5,6].

FACTORS INFLUENCING SELECTION OF POLYMER FOR SR/CR DOSAGE FORMS:

Generally rheological behavior and possible interactions with the drug and other components of the dosage form are major factors to be considered. Other factors are,

1. **Physicochemical Compatibility:**

The physicochemical type of polymers and other ingredients in the system must be mutually compatible. Knowledge of charge on the particle surface is helpful in anticipating changes in the stability character.

2. Biological Compatibility:

It is obvious that certain polymeric agents will be removed from consideration depending on the route of administration or application. The vulnerability of materials of natural organ to microbiological attack is often cited[7,8].

CAPSULES OF MANUFACTURING OPERATIONS:

The manufacturing operations can be broadly divided into the four phases.

(a) Drug preparation
(b) Capsule filling
(c) Capsule finishing
(d) Capsule packing

ENCAPSULATION PROCESS:

Two general methods are involved in encapsulation process.

1. Hand filling
2. Capsule filling machine

POWDER FILL:

1. ACCOFIL:

Powder is charged into a hopper and is pre-conditioned by mixing and/or agitator blade(s) to assist powder delivery and flow. The pre-determined amount of powder is drawn into the fill wheel ports with vacuum from the supply hopper. The powder is held by vacuum in the fill wheel ports until it is indexed into and dispensed into the container by use of compressed air.

2. AUGER:

Powder is charged into a hopper and is pre-conditioned by mixing and/or agitator blade(s) to assist powder delivery and flow. An auger is utilized to deliver the powder from the hopper into the container using a predetermined degree of revolution[9,10].

PELLETIZATION:

METHODS USED FOR PELLETS PREPARATION:

Methods for preparing pellets include[7]

a) Compaction
b) Powder layering or Drug layering

Compaction:

In the compaction techniques, extrusion and spheronization is the most popular method. Recently, however, melt pelletization has been used frequently in making compaction pellets using a different type of equipment, e.g. a high-shear mixer. Other pelletization methods such as globulation, balling and Compression are also used in development of pharmaceutical pellets although in a limited scale.

Powder layering:

Powder layering involves the deposition of successive layers of dry powders of drugs and excipients on preformed nuclei or cores with the help of binding liquids. As powder layering involves simultaneous application of binding agents and dry powders, hence it

requires specialized equipments like spheronizer. The primary requirement in this process is that the product container should be solid walls with no perforation to avoid powder lose beneath the product chute before the powder is picked of by the wet mass of pellets that is being layered[11,12].

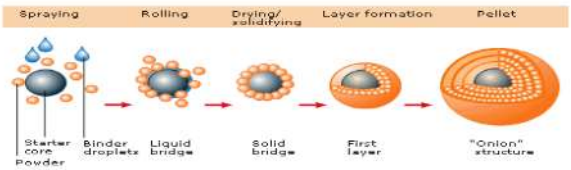

Figure 1 Principle of the Powder Layering Process

Solution (or) Suspension layering:

Solution (or) Suspension layering involves the deposition of successive layers of solution or suspensions of drug substances and binder over the starter (or) non-pareil seeds, which is an inert material or crystals (or) granules of the same drug. In fact the coating process involved in general is applicable to solution or suspension layering technology. Consequently conventional coating pans, fluidized beds, centrifugal granulators, wurster coaters have been used successively to manufacture pellets by this method. The efficiency of the process and the quality of the pellets produced are in part related to the type of equipment used.

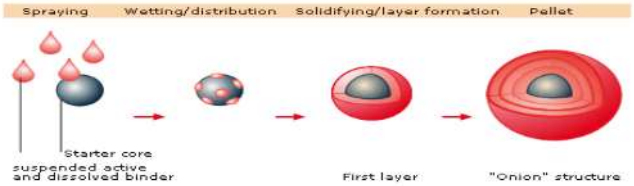

Figure 2 Principle of the Suspension (Or) Solution Layering Process

Pelletization by Extrusion and Spheronization:

The process involves first making the extrudes from the powder material and then converting the extrudes into beads using the spheronizer. The powder material could be any kind of powder (drug powder, Ayurvedic powder, food ingredient powder, detergent powder, nuclear powder etc). Beads as fine as 0.6mm can be made[13,14].

AIM AND OBJECTIVE OF WORK

The aim of the present research is to develop and evaluate a better sustained release multiple unit pellets (MUP) formulation of Tramadol hydrochloride.

FORMULATION OF TRAMADOL HCl SR PELLETS:

In the present study 6 formulations of Tramadol HCl SR pellets were prepared and the formulations composition was mentioned in the Table no.3.

PROCEDURE FOR THE PREPARATION OF TRAMADOL HYDROCHLORIDE SUSTAINED RELEASE PELLETS[39]:

Step 1: DISPENSING:

Weigh the raw materials according to the manufacturing work order into double lined poly bags and affix dispensing labels with all details.

Step 2: **PULVERISATION AND BLENDING**:

Pulverize the Tramadol HCL powder thoroughly and collect in double lined Polybags.

- Sieve through #30 mesh by using sifter
- Load the sifted material along with the starch in double cone blender and mix for 30 minutes.

Step 3: DRUG LOADING SOLUTION PREPARATION:

PVP K90 is dissolved in isopropyl alcohol under stirring

Step 4: DRUG LOADING:

Load the non-pariel seeds into coating pan and wet it by spraying the Solution from step-3 and dust the blend powder till material stick to wet pellets, to form round spheres and repeat the operation till blend powder completes.

Step 5: **DRYING AND SIFTING OF DRUG COATED PELLETS**:

- Initially dry the pellets under the current of air for 30min switch on the heaters and maintain temperature from 28°c-32°c. Dry the pellets till the moisture content of pellets reduce to 1.5%.
- Shift the pellets from sieve #18 mesh, collected the #25 mesh passing Sifting the #18 mesh passing through #25 mesh retained pellets and Labelled as 18/25 fraction pellets.

Step 6: PREPARATION OF S.R COATING SOLUTION:

- Take isopropyl alcohol and methylene di chloride in a stainless steel container to this add Acetone under stirring continuously.
- To the above solution add ethyl cellulose by stirring
- Filter the solution through nylon mesh to get a uniform solution.

Step 7: SR COATING:

Load the drug pellets into Fluidized bed coater and spray the SR coating coating Solution by using Fluidized bed coater Maintain the required conditions in coater[15,16].

TABLE. 1 INPROCESS PARAMETERS FOR SR COATING

Process parameters	Range
Inlet temperature	38-42^{0}C
Product temperature	32-36^{0}C
CFC	800-2500
Atomization	1-3
Spray pressure(Barr)	3-4
Peristaltic pump speed	12-18rpm
Spray rate(mg/min)	8-12
Wruster height(mm)	20-60

Step 8: DRYING AND SIFTING FOR SR COATED PELLETS:

- Initially dry the pellets under the current of air for 30min by using heaters and maintain temperature from 28°c-32°c. Dry the pellets till the moisture content of pellets reduce to 1.5%.
- Sift the SR coated pellets from sieve #12 mesh , collect #12 mesh passings.sifting the #12 mesh passing through #16 mesh retained pellets and labeled as 12/16 fraction pellets.

Totally 6 Formulation trails were done using the same procedure. During all the stages of the manufacturing process, temperature and humidity was maintained at 25 ± 5^{0}C and 50 ± 10 % RH. To optimize the formulation, the capsules were assay by U.V Spectroscopic method and drug release study.

The formula of Trial 5 was optimized and selected for evaluation studies. By using the same formula as that of Trial 5 batch that was taken for the stability study purpose.

Step 9: Filling: Filling of the pellets into capsules by manually[17,18].

LOADING OF AMBROXOL HCL SR PELLETS IN CAPSULES:

Procedure:

- Size'2' capsules were selected for capsule formulation
- The pellets were loaded in hard gelatin capsules No-2 by manual filling because it is a lab scale batch.
- Coated pellets were transferred into capsules by spreading it into equal quantities equivalent to 100 mg Tramadol HCL .As per the above procedure, drug loading was carried out for 6 trails[19,20].

RESULTS

Table 2 Preformulation Study of Active Pharmaceutical Ingredient

Characteristics	Results
Physical appearance	A white (or) almost white powder, odourless.
Solubility	Sparingly soluble in water and soluble in Methanol, practically soluble in Methylene chloride.
Bulk density	0.72gm/ml
Tap density	0.84gm/ml
Compressibility index	14.28%
Melting point	180-184^{0}C
Molecular weight	299.84.

Table. 3 Preformulation Characteristics

Formulations	Angle of Repose (°)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Compressibility Index (%)	Moisture Content (%)
F1	28.7	0.72	0.86	16.27	2.41
F2	26.4	0.78	0.89	12.35	2.42
F3	27.3	0.74	0.86	13.95	1.92
F4	25.9	0.71	0.87	18.39	2.63
F5	28.1	0.72	0.84	14.28	2.34
F6	26.5	0.73	0.85	14.11	2.45

Table. 4 Dissolution Studies:

Dissolution Time(hr)	Percentage Drug Release (%)						
	F1	F2	F3	F4	F5	F6	Innovator
1	28.4	23.4	21.9	18.8	**18.4**	11.4	**18.6**
2	40.8	39.4	36.5	33.2	**30.6**	27.4	**31.4**
4	59.3	57.3	54.1	49.3	**45.2**	40.1	**45.6**
8	73.9	72.6	69.4	58.3	**55.4**	52.2	**56.1**
12	89.6	87.4	85.8	85.6	**83.9**	75.1	**84.2**
24	96.4	95.1	94.6	93.9	**92.6**	82.4	**93.1**

Table. 5 Mean Dissolution Time (MDT) of the Formulations:

Formulation	MDT (Hr)
F1	4.723
F2	4.919
F3	4.97
F4	5.91
F5	6.19
F6	6.27

Table. 6 Comparison of Dissolution Profiles by Similarity Factors:

Formulation	Difference Factor (f_1)	Similarity Factor (f_2)
F1	14	56
F2	9	67
F3	18	46
F4	13	56
F5	**4**	**71**
F6	24	46

Table. 7 Correlation Coefficient of Drug Release:

Formulation	Zero Order		Higuchi		Kosemayer plot			First Order		Hixon Crowl	
	r	k	R	k	r	n	k	r	k	r	K
F1	0.861	5.051	0.981	20.38	0.981	0.92	9.099	0.987	0.037	0.964	0.124
F2	0.862	5.622	0.972	20.43	0.972	0.945	8.394	0.953	0.032	0.928	0.118
F3	0.934	4.111	0.992	20.41	0.978	0.955	7.961	0.988	0.032	0.982	0.116
F4	0.927	6.136	0.976	20.34	0.978	0.971	7.227	0.979	0.043	0.966	0.115
F5	0.901	6.257	0.984	20.11	0.984	0.972	6.934	0.991	0.051	0.972	0.111
F6	0.815	6.149	0.936	18.41	0.964	1.014	5.675	0.895	0.029	0.868	0.085

Table. 8 Evaluation of Capsules:

Formulation	Weight Variation	Maximum Deviation (+ve)	Minimum Deviation (-ve)
F1	269.4	+10.95	-9.87
F2	268.8	+3.170	-3.57
F3	273.1	+2.80	-2.48
F4	271.6	+2.56	-2.50
F5	270.4	+2.30	-2.25
F6	273.9	+2.16	-2.11

SUMMARY & CONCLUSION

The present work aimed at developing SR pellets of Tramadol HCl by Wurster process. FTIR studies showed no unacceptable extra peaks which confirm the absence of chemical interaction between the drug and polymer. Angle of repose, tapped density, bulk density values for the formulations were within the range which indicates that pellets prepared by Wurster process were satisfactory for further studies. The percentage drug content of Tramadol was determined by extraction with methanol and analyzed by using UV-visible spectrophotometer at 271nm. After 12th hour the percentage drug release from the formulations were 89.6%, 87.4%, 85.8%, 85.6%, 83.9%, 75.1% for the formulations containing EC7cps 1%,1.5% , 2% and EC50cps 2.5%, 5% and 7.5% respectively. The dissolution profile was shown in Fig.2.The burst release of Tramadol HCl from formulations with EC 50cps is comparatively lower than the one with EC 7cps, due to the fact that EC 50cps is more viscous and release retarding capacity is more when compared to EC 7cps. Formulation F5 was identified to be the best as it matches well with the innovator (f2 = 71). The release mechanism was explored and explained with Higuchi and Hixoncrowel equations, which indicates that pellets followed diffusion and erosion mechanisms for drug release.

Accordingly, it can be concluded that the F5 (5%w/w EC 50cps) is robust one and the performance is less likely to be affected by the various factors studied. The formulations were kept at stability studies according to ICH guidelines for 3 months, which showed that all the formulations were stable.

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