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Research Article

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FORMULATION AND EVALUATION OF BUDESONIDE CONTROLLED RELEASE CAPSULES BY SUSPENSION LAYERING METHOD

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ABSTRACT

Multiunit pellet systems (MUPS) are an approach to develop capsule formulation for controlled release. Capsule containing MUPS, when administered rapidly disperses in the GIT, each pellet act as a sub unit, consequently as a separate drug delivery system. Controlled release pellets which delivers the drug at a predetermined rate, at a predetermined region, reduces peak plasma fluctuations, consequently potential side effects can be minimized. MUPS have good desirable transit time and reduced chance of gastric irritation owing to the localization of drug delivery. Budesonide rapidly absorbed after oral administration, but has poor systemic availability (about 10%) due to extensive first pass metabolism in the liver by Cyp3A4. by using controlled release form which release the drug at ileum or ascending colon region (pH>5.5) by minimizing the drug release in the stomach. By using extended release form there is a reduction in dosing frequency, reduction in plasma fluctuations consequently potential side effects can be minimized.

KEYWORDS

Multiunit pellet systems, suspension layering method, Budesonide, controlled release.

1. INTRODUCTION

The overall action of a drug molecule is dependent on its inherent therapeutic activity and the efficiency with which it is delivered to the site of action. An increasing appreciation of the latter has led to the evolution and development of novel drug delivery systems (NDDS), aimed at performance enhancement of potential drug molecules. Novel drug delivery systems (NDDS) are the key area of pharmaceutical research and development. The reason is relatively low development cost and time required for introducing a NDDS ($20- 50 million and 3- 4 years, respectively) as compared to new chemical entity (approximately $500 million and 10- 12 years, respectively). The focus in NDDS includes design of NDDS for new drugs on one hand and on the other NDDS for established drugs to enhance commercial viability. Oral route remains one of the most natural routes of drug administration and has seen remarkable accomplishments in the last couple of decades towards optimization of oral delivery of drug molecules. Oral ingestion is one of the oldest and most extensively used routes of drug administration, providing a convenient method of effectively achieving both local and systemic effects.

Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the system can provide some control, whether this is of a temporal or spatial nature, or both of drug release in the body, or in other words, the system is successful maintaining constant drug

levels in the target cells or tissues, it is considered a controlled release system.

Potential advantages of controlled drug therapy

All controlled release products share the common goal of improving drug therapy over that achieved with their non-controlled counter parts. This improvement in drug therapy is represented by several potential advantages, which include:

- Avoid patient compliance problems.
- Reduction in frequency of dosing.
- Employ minimum total drug.
- Minimize or eliminate local side effects.
- Minimize or eliminate systemic side effects.
- Cure or control condition more promptly.
- Reduce fluctuations in drug level.
- Improve bioavailability of some drugs.
- Minimize drug accumulation with chronic dosing.
- Improve efficacy in treatment.
- Make use of special effects e.g. sustained release aspirin for morning relief of arthritis by dosing before bedtime.

Mups for CR Systems

Oral modified drug delivery systems can be classified into two broad groups:

1. Single Unit dosage forms.
2. Multiple unit particles.

Multiple unit particles (MUPS), such as granules, pellets, or mini tablets

The concept of MUPS was initially introduced in 1950s. The production of MUPS is a common strategy to control the release of drug as shown by the reproducibility of the release profiles when compared to the ones obtained with SUDFS. The concept of MUPS is characterized by the fact that the dose is administered as a number of sub units, each one containing the drug. Then the dose is sum of the quantity of the drug in each sub unit and the functionality of individual sub-units. In contrast to Monolithic dosage forms multiple unit dosage forms offer several advantages. Controlled release systems can be developed by multi-unit dosage forms. The capsule comprised of a multiple unit pellets when administered, freely disperse in the GIT as a sub unit, each pellet acting as a separate drug delivery unit. Thus, maximizing drug absorption and reducing the peak plasma fluctuations, consequently, potential side effects can be minimized without imparting drug bioavailability.

Methods of preparation of multiple unit dosage forms

To understand the complete strategy of the multiple unit dosage forms, it is necessary to have a brief idea regarding how pellets are prepared and principles involved in it.

Pelletization

An agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free-flowing, spherical units, referred to as pellets, where size range typically from 0.5-1.5mm.

The most widely used pelletization processes in pharmaceutical industries are,

- Balling
- Cryopelletization
- Spray drying and spray congealing
- Solution, Suspension and powder layering
- Extrusion and spheronization.

2. MATERIALS AND METHODS

2.1 Materials

Hydroxy propyl methyl cellulose E5,Tween 80, Ethyl cellulose 7cps, Hydroxy propyl methyl cellulose pthalate 55s, Eudragit L-100 55, Aqua coat ECD, Diethyl phthalate, Triethyl citrate, Cetyl alcohol, Talc, Povidone, Isopropyl alcohol

2.2 Methods

Solution/suspension layering by matrix layer formulation

Drug and polymer matrix layering on sugar spheres

The required quantity of sugar spheres (18/20#) were weighed and transferred into a fluidized bed processor and required quantity of triethyl citrate and polysorbate – 80 were dissolved in specified volume of water. Required volume of Aquacoat ECD (signet chem. Corp.) was added to above solution under continuous stirring. Later required quantity of budesonide was dispersed in above suspension by stirring. This suspension was sprayed on sugar spheres by bottom spray technique. This drug and polymer matrix layered pellets were used for enteric coating.

Enteric coating of polymer coated pellets by using HPMCP-55s

The required polymer coated pellets were loaded into the FBC and required quantity of diethyl phthalate and cetyl alcohol were dissolved in specified volume of isopropyl alcohol and acetone mixture. Later, Hydroxy propyl methyl cellulose phthalate 55s, dissolved in above solution and stirred for 20min. required quantity of talc was added to solution by stirring. The solution was sprayed on polymer coated pellets by bottom spray FBC.

Enteric coating by using Eudragit L-100-55

The required quantity of drug-polymer matrix layered pellets were loaded into the FBC and required quantity of triethyl citrate and Eudragit L-100-55 were dissolved in specified volume of isopropyl alcohol and acetone mixture under continuous stirring for 20min. later required quantity of talc was added to above solution on drug-polymer matrix layered pellets in bottom spray FBC.

Composition of drug and polymer matrix coated pellets for the formulation trials (F1-F6)

Name of the Excipients	Weight of the Excipients (gm/600gm batch)					
% of polymer	F1 (2.0%)	F2 (2.0%)	F3 (1.75%)	F4 (1.75%)	F5 (1.5%)	F6 (1.5%)
Budesonide (1%)	6.0	6.0	6.0	6.0	6.0	**6.0**
Sugar spheres	575	575	575	575	575	**575**
Aquacoat ECD	12.0	12.0	10.5	10.5	9.0	**9.0**
Polysorbate (10% of Drug)	0.60	0.60	0.60	0.60	0.60	**0.60**
Tri ethyl citrate (20% of polymer)	2.40	2.40	2.10	2.10	1.80	**1.80**
Water	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**

Note: # the material balance would become 600gm only after enteric coating step.

* Aquacoat ECD is a 30% suspension contained ethyl cellulose (30%), sodium lauryl sulphate (0.9-1.7%), cetyl alcohol (1.7-3.3%), (FMC Biopolymers)

Composition of enteric coated pellets for the formulation trials (F1-F6)

Name of the Excipients	Weight of the Excipients (in grams)					
	F1 (HPMCP Coated)	F2 (Eudragit coated)	F3 (HPMCP Coated)	F4 (Eudragit coated)	F5 (HPMCP Coated)	F6 (Eudragit coated)
Polymer coated pellets	520	520	520	520	520	520
Hydroxy propyl methyl cellulose 55s	72.8	-	62.4	-	52	-
Eudragit L-100 55	-	72.8	-	62.4	-	52
Diethyl phthalate(10% of polymer)	7.28	-	6.24	-	5.2	-
Triethyl citrate (10% of polymer)	-	7.28	-	6.24	-	5.2
Cetyl alcohol (5% of polymer)	3.64	-	3.12	-	2.6	-
Talc(3% of polymer)	2.18	2.18	1.87	1.87	1.56	1.56
Acetone:Iso propyl alcohol(3:1)	360:120	360:120	360:120	360:120	360:120	360:120

3. RESULTS AND DISCUSSION

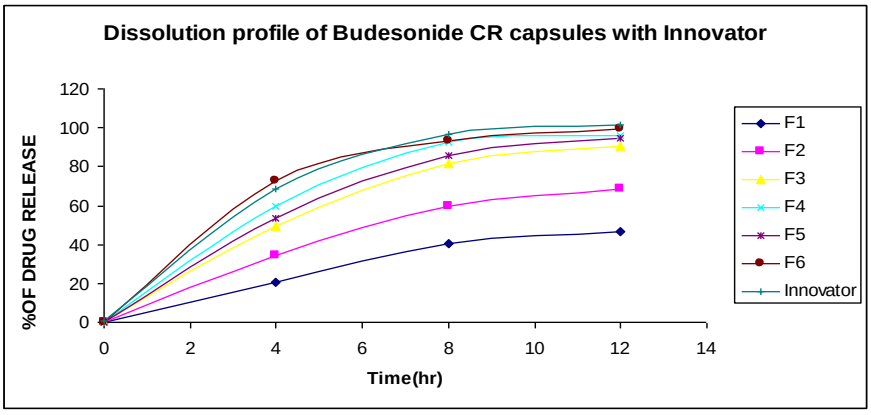
Compatibility studies at different temperatures and relative humidity showed that drug itself was stable at higher temperature and relative humidity, as well as compatible with all above used excipients**.**

From the drug release profile and histograms, it was found that Eudragit L100 55 enteric coated formulation (F1) released more drug in comparison with HPMC phthalate enteric coated formulation (F2). Thus, the nature of the enteric polymer could also affect the release rate from dosage form. However, F1 and F2 were not matching in their release profile with that of innovator, failing at all time intervals. From the drug release profile and histograms, it was found that Eudragit L100 55 enteric coated formulation (F4) released more drugs in comparison with HPMC phthalate enteric coated formulation (F3). Thus, the nature of the enteric polymer could also affect the release rate from dosage form. From the drug release profile and histograms, it was observed that Eudragit L100 55 enteric coated formulation (F5) released more drug in comparison with HPMC phthalate enteric coated formulation (F6). Thus, the nature of the enteric polymer could also affect the release rate from dosage form. Drug release from F5(1.5%) was not matching with that of innovator, failing at all time intervals as per innovator's profile. Drug release from F6(1.5%) was matching with that of innovator at al time points, and was considered as best formulation when with other formulations. Formulation F4 was also matching with that of innovator at 3rd and 4th time points, but F6 was matching with that of innovator at all time intervals. So, formulation F6 was found suitable for budesonide CR 3mg capsules preparation. In Stability studies observed that both accelerated and long term stability studies were conducted for two months. During this study, the formulation F6 was found to be stable and no differences in the assay and release characteristics were noticed.

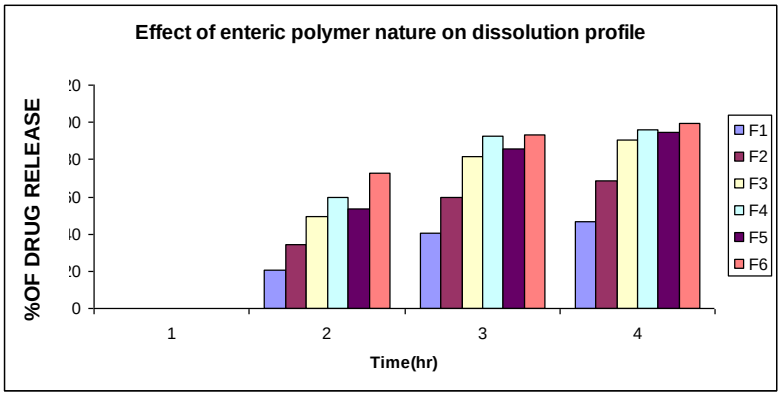
Percentage drug release of budesonide CR capsules 3mg in different trials (F1-F6) comparison with that of innovator.

Buffer	Sample time (hr)	Cumulative percent drug release ± SD						
		F1	F2	F3	F4	F5	F6	Innovator
pH 1.2 buffer	2hr	0	0	0	0	0	0	0.9±0.05
pH 7.5 buffer	2hr	20.4±1	34.4±1.4	49.2±1.2	59.7±2.7	53.5±1.32	73±1.2	68.9±0.64
pH 7.5 buffer	6hr	40.7±1.5	59.4±1.7	81.3±2.3	92.4±1.55	85.4±0.73	93.5±1.47	96.6±0.72
pH 7.5 buffer	10hr	46.9±0.7	68.5±3.1	90.2±1.0	95.9±1.45	94.8±0.67	99.5±0.61	101.2±1.34

***In vitro* dissolution profile if budesonide CR capsules 3mg in different trials (F1-F6) comparison with Innovator**



Histogram showing the effect of polymer nature on drug release



4. CONCLUSION

The study was undertaken with an aim to formulate budesonide controlled release capsules. The drug budesonide is corticosteroid and used for the treatment of Crohn's disease. Before going to develop the formulation, a detail product literature review was carried out to know about the innovator's (type of dosage form available in market, weights, all other parameters and excipients used) product and the patent status of the drug. Preformulation study involving drug – excipients compatibility was done initially and results indicated the compatibility with all the tested excipients. The study was carried out by solution/suspension matrix layering method. In this method first drug and polymer solutions were mixed, coating was done on the sugar spheres; further enteric coating was done on polymer matrix coated pellets. Different trials were conducted with various percentages of polymer in first stage and second stage (during enteric coating), and the formulation was finally optimized based on the drug release profile.

Pellets were evaluated by *in vitro* dissolution. These studies revealed that the F6 pellets were found to be release the drug almost comparable to that of innovator's product. Further, the F6 formulation was subjected to release studies at different pH conditions and found to have similar release profile as that of innovator. The *in vitro* dissolution tests were performed and f2 values were calculated for all trials. Dissolution profile of formulation F6 matched with that of the innovator's product and f2 value was satisfactory.

Stability studies were also performed; both accelerated and long term stability studies were conducted for two months. During this study, the formulation F6 was found to be stable and no differences in the assay and release characteristics were noticed.

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