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EFFECT OF PLASTICIZER ON STABILITY OF BUDESONIDE (C.R) MUPS PREPARED BY AQUEOUS POLYMER LAYERING

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ABSTRACT: The present study was designed to investigate the effect of two different types of plasticizers, i.e., Triethyl citrate (TEC) and Acetyl tri butyl citrate on the *in vitro* release kinetics of Budesonide from sustained-release pellets during initial and stability conditions. Ethyl cellulose aqueous dispersion (Aqua coat ECD 30) is used as the release-retarding polymer. Both plasticizers were used at 10 % to 30% (*w*/*w*) of Aqua coat ECD 30. Sugar spheres #16/20 were used as core pellets. Dissolution study was performed by using USP apparatus II with sinker in 0.1 N HCl followed by 7.5 pH phosphate buffer. Trails planned with water insoluble plasticizer like acetyl tri butyl citrate showed comparative dissolution profile with innovator during initial condition but during accelerated stability conditions like 40ºC 75% RH for 6M dissolution profile was found to be on lower side when compared with innovator. Hence trails were planned with water soluble plasticizer like tri ethyl citrate showed comparable dissolution profile with innovator during initial and stability conditions. Different trails were planned with different concentrations of tri ethyl citrate from 10% to 50 % w/w of the polymer. Among them tri ethyl citrate with 30% w/w of polymer showed optimum dissolution profile during initial and stability conditions. Further increase in tri ethyl citrate concentration to 50% w/w of polymer dissolution profile was found to be in lower side in initial condition.

INTRODUCTION: Sustained release systems include any drug delivery system achieves release of drug over an extended period of time, which not depends on time. Hydrophilic polymer matrix is widely used for formulating a Sustained dosage form. The role of ideal drug delivery system is to provide proper amount of drug at regular time interval & at right site of action to maintain therapeutic range of drug in blood plasma.[1]

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Advantages of Sustained/Controlled release drug delivery system over the conventional dosage form:

- ✓ Reduced dosing frequency.
- ✓ Dose reduction.
- ✓ Improved patient compliance.
- ✓ Constant level of drug concentration in blood plasma.
- ✓ Reduced toxicity due to overdose.
- ✓ Reduces the fluctuation of peak valley concentration.
- ✓ Night time dosing can be avoided. [2]

Controlled release: It includes any drug delivery system which releases the drug pre determined rate over an extended period time.

Limitation of oral conventional dosage form:

1. Poor patient compliance, increased chances of missing the dose of a drug with short half life for which frequent administration is necessary.
2. The unavoidable fluctuations of drug concentration may lead to under medication or over medication in narrow therapeutic index drug.
3. A typical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition impossible.[3, 4]

Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free flowing, spherical or semi spherical units, referred to as pellets. Pellets range in size, typically, between 0.5 – 1.5 mm, though other sizes could be prepared. Pellets can be prepared by many methods, the compaction and drug-layering techniques being the most widely used today. Regardless of which manufacturing process is used, pellets have to meet the following requirements.

Advantages of Pellets:

- ✓ They can be divided in to desired dosage strength without process or formulation changes.
- ✓ When pellets containing the active ingredient are in the form of suspension, capsules, or disintegrating tablets, they offer significant therapeutic advantages over single unit dosage forms**.**
- ✓ They can also be blended to deliver incompatible bioactive agents.
- ✓ They can also be used to provide different release profile at the same or different sites in the gastrointestinal tract.
- ✓ Pellets offer high degree of flexibility in the design and development of oral dosage form like suspension, sachet, tablet and capsule.
- ✓ Pellets disperse freely in gastro intestinal tract (GIT), maximize drug absorption, and minimize local irritation of the mucosa by certain irritant drugs.[5]

Multiparticulate Drug Delivery System:

Oral dosage form can be broadly classified into two categories: Single-unit and Multiple-unit dosage forms. The single-unit dosage forms include matrix tablet or coated/uncoated tablet or capsules. The multiple-unit dosage forms consist of pellets or microencapsulated drug filled in a capsule or compressed into a tablet. The basic concept of multiple-unit systems is that the dose of the active ingredient is released by the individual subunits like pellets, and the functionality of the entire dose depends on the quality of the subunits. The idea behind designing multiparticulate dosage forms is to build up a reliable formulation which has all the advantages of single unit formulations without danger of modification in drug release profile and formulation behavior owing to unit to unit variation.

These delivery systems are mainly reservoir type of oral dosage forms having multiplicity of small distinct units, each having some preferred characteristics. In these types of drug delivery systems, the dosage of the drug substances is separated on a plurality of subunit. Multiparticulate dosage form is pharmaceutical formulations where the active substance is in the form of number of small independent subunits. They give many advantages over single-unit systems due to their small size. Drug safety may also be augmented by using multiparticulate dosage forms, mainly for modified release systems. To deliver the projected entire dose, these subunits are packed into a capsule or compressed with added excipients to form a tablet.[6, 7]

Advantages:

- ✓ Predictable, reproducible and short gastric residence time
- ✓ Less inter- and intra-subject variability
- ✓ Improve bioavailability
- ✓ Reduced adverse effects and improved tolerability
- ✓ Limited risk of local irritation

- ✓ No risk of dose dumping
- ✓ Flexibility in design
- ✓ Ease of combining pellets with unlike compositions or release patterns.
- ✓ Improve stability
- ✓ Improve patient comfort and compliance
- ✓ Achieve a unique release pattern
- ✓ Extend patent protection, globalize product and overcome competition

Drawbacks:

- ✓ Low drug loading
- ✓ Proportionally higher need for excipients
- ✓ Lack of manufacturing reproducibility and efficacy
- ✓ Large number of process variables
- ✓ Multiple formulation steps
- ✓ Higher cost of production
- ✓ Need of advanced technology
- ✓ Trained/skilled personal needed for manufacturing.[8]

Ideal Characteristics of MUPS:

1. Should maintain all the tablet properties.
2. Pellets should not show any interaction like developing electrostatic charges; during compression.
3. The pellets should not show any deviation in its release even after compression.
4. The coated pellets during the process of compression should not fuse into a no disintegrating matrix and should not lose its coating integrity either by breaking or cracking or rupturing the coating layer(s) or pinholes and other imperfections.
5. Like tablets, MUPS should have ease to withstand physical parameters, stability, packing storage and transportation. The dosage form must disintegrate rapidly into individual pellets in gastrointestinal fluids.[9]

MATERIALS AND METHODS:

Materials:

Budesonide (Aarti Industries), Sugar spheres #16/20(Signet), Polysorbate- 80(Croda Singapore Pvt ltd), Aqua coat ECD30(FMC Bio Polymer), Triethyl citrate(Vertellus Performance Materials Inc), Acetyl tri butyl citrate(Vertellus Performance Materials Inc), Talc(Luzenac), Simethicone(Dow corning India Pvt Ltd), Eudragit L100-55(Evonik Industries), sodium hydroxide(Merck), purified water.

Methods:

Suspension layering on multi-unit inert core pellets by using Fluid Bed Processor

Drug and polymer matrix layering on sugar spheres:

The required quantity of sugar spheres (16/20#) were weighed and transferred into a fluidized bed processor and required quantity of Triethyl citrate or acetyl tri butyl citrate and Polysorbate – 80 were dissolved in specified volume of water. Required volume of Aqua coat ECD (FMC Bio Polymer.) 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. Composition of drug and polymer matrix coated pellets for formulation trails were given in **Table 1**.

TABLE 1: COMPOSITION OF DRUG AND POLYMER MATRIX COATED PELLETS FOR THE FORMULATION TRIALS (F1-F7)

Name of excipient	Weight of the excipients (mg/unit)						
Trails (%plasticizer)	**F1 (10%)**	**F2 (20%)**	**F3 (30%)**	**F4 (10%)**	**F5 (20%)**	**F6 (30%)**	**F7 (50%)**
Sugar spheres #16/20	300	300	300	300	300	300	300
Budesonide	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Aqua coat ECD 30	6.60	6.60	6.60	6.60	6.60	6.60	6.60
Polysorbate-80	0.50	0.50	0.50	0.50	0.50	0.50	0.5
Tri ethyl citrate	…	…	…	0.66	1.32	1.98	3.3
Acetyl tri butyl citrate	0.66	1.32	1.98	…	…	…	…
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s

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

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, Eudragit L-100-55, sodium hydroxide and simethicone were dissolved in specified volume of purified water under continuous stirring for 20min. later required quantity of talc was added to above solution and it was coated on drug-polymer matrix layered pellets in bottom spray FBC. Composition of enteric coated pellets for the formulation trials were given in Table: 2.

TABLE 2: COMPOSITION OF ENTERIC COATED PELLETS FOR THE FORMULATION TRIALS (F1-F7)

Name of Excipient	Weight of the Excipients (15% build up)
Trails	F1- F7
Eudragit L100-55	28.34
Sodium hydroxide	0.36
Tri ethyl citrate	2.92
Poly sorbate-80	0.82
Simethicone	0.02
Talc	14.24
Purified water	q.s

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**.**

Trails from F1 to F3 were planned with acetyl tri butyl citrate as a plasticizer. Dissolution profile of F1 trail was found to be in lower side compared with innovator but dissolution profiles of F2 & F3 were found to be matching with the innovator dissolution profile in 0.1 N HCL followed by 7.5 pH phosphate buffer in initial condition but during stability in 40ºC/75%RH for 2 months dissolution profile was found to reducing compared to initial data.

Hence next trails (F4 to F7) were planned with tri ethyl citrate as a plasticizer. Dissolution profile of F4 (10% w/w) was slightly in higher side compared with the innovator during initial condition but in stability dissolution profile was found to be in lower side. Dissolution profile of F5 (20% w/w) was slightly in higher side compared with the innovator during initial condition but in stability dissolution profile was found slightly in lower side. But dissolution profile of F6 (30% w/w) was found to be matching with the innovator dissolution profile in 0.1 N HCL followed by 7.5 pH phosphate buffer in both initial condition and accelerated stability condition 40ºC/75%RH for 6 months. F7 trail planned with 50% w/w plasticizer produced completely lower dissolution profile compared with innovator. Hence from above studies 30 % w/w Triacetin as a plasticizer was selected as optimum concentration.

TABLE 3: PERCENTAGE DRUG RELEASE OF BUDESONIDE CR CAPSULES 3MG IN DIFFERENT TRIALS (F1-F3) COMPARISON WITH THAT OF INNOVATOR

Time in hrs	Innovator		F1		F2		F3	
	Initial	stability	Initial	stability	Initial	stability	Initial	stability
Acid-2hr	0	0	0	0	0	0	0	0
7.5 pH phosphate Buffer, 1000 ml, paddle with sinker ↓								
1 hr	54	53	39	25	51	23	60	31
2 hr	72	72	68	42	65	39	79	52
4 hr	81	82	75	61	80	69	85	70
6 hr	85	84	80	70	87	70	89	72
8 hr	87	87	81	71	88	75	92	76

TABLE 4: PERCENTAGE DRUG RELEASE OF BUDESONIDE CR CAPSULES 3MG IN DIFFERENT TRIALS (F4-F6) COMPARISON WITH THAT OF INNOVATOR

Time in hrs	Innovator		F4		F5		F6		F7
	Initial	stability	Initial	stability	Initial	stability	Initial	stability	Initial
Acid-2hr	0	0	0	0	0	0	0	0	0
7.5 pH phosphate Buffer, 1000 ml, paddle with sinker ↓									
1 hr	54	53	68	45	56	49	**58**	**56**	29
2 hr	72	72	79	65	70	70	**75**	**73**	36
4 hr	81	82	85	75	83	79	**85**	**85**	39
6 hr	85	84	89	82	90	83	**88**	**86**	45
8 hr	87	87	92	83	91	83	**90**	**89**	46

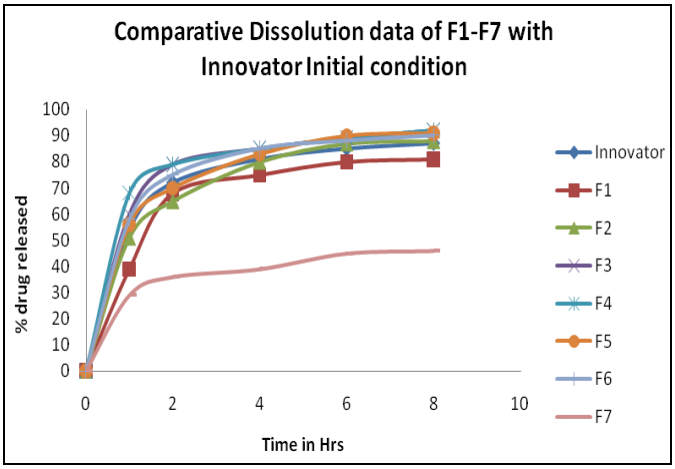

FIGURE 1: COMPARATIVE DISSOLUTION DATA OF F1-F7 WITH INNOVATOR INITIAL CONDITION

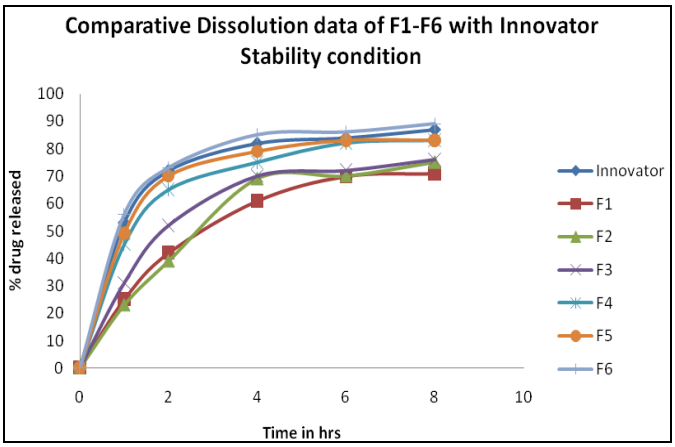

FIGURE: 2 COMPARATIVE DISSOLUTION DATA OF F1-F7 WITH INNOVATOR STABILITY CONDITION

CONCLUSION: The main aim of the study was to investigate the effect of two different types of plasticizers, i.e., Triethyl citrate (TEC) and Acetyl tri butyl citrate on the *in vitro* release kinetics of Budesonide from sustained-release multi unit pellets during initial and stability conditions.

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 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 two different types of plasticizers like Acetyl tri butyl citrate and Tri ethyl citrate and at different concentrations from 10% to 30 % w/w of Aqua coat ECD 30. Trails from F1-F3 were planned with Acetyl tri butyl citrate as a plasticizer among them F1 (10% w/w Plasticizer) data was not matching with innovator, F2 & F3 (20% & 30w/w Plasticizer) dissolution data were matching with innovator in initial condition but in accelerated stability condition dissolution data was found to reducing compared with innovator.

Hence further trails F4-F7 were planned with hydrophilic plasticizer like Tri ethyl citrate. Among them F4 (10% w/w Plasticizer) & F5 (20% w/w Plasticizer) data were not matching with innovator (higher side) in initial, but during stability dissolution was found to slightly lower side. F6 (30% w/w Plasticizer) dissolution data was matching with innovator in both initial condition and accelerated stability condition (40ºC/75% RH-6M). F7 which was formulated with 50% w/w plasticizer dissolution profile was found to be in lower side in initial condition only. From this study it was concluded that trail F6 (30% w/w Plasticizer) was found to be stable in both initial & stability which was formulated with tri ethyl citrate as a Plasticizer.

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