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PROCESS & VARIATION IN EFFERVESCENTFORMULATION: A review

ReviewArticle

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Abstract
Oral dosage forms are the most popular way of medication but it has some disadvantages like slower absorption rate. This can be avoided by intake of liquid dosage forms. However, it has been found that most of the APIs are unstable in liquid formulation. So, effervescent form of drug delivery has evolved as an alternate way of medication in which drug are found to be stable as well as easy to administer. In this present review, we are going to discuss about various manufacturing processes and their variations.
Key word: effervescent formulations, manufacturing process, variations, Topo technology.

INTRODUCTION

Now-a-days, effervescent formulation is very popular way of medication as pediatric and geriatric patients found it very easy to intake. Patient can be administered by appropriate butrelatively large dose than conventional dosage forms [1, 2, 3, 4, and 5].Effervescent formulations are used as dentifrices,mouthwashes tablets [6]sustain release drug delivery system [7],tooth cleansing agent, [8] antacids, and analgesics [9]. It is also manufactured in different form like general tablets and chewable tablets (effervescent dentifrices)[10]. Generally, these are uncoated tablets which release carbon dioxide as theycomes in contact with moisture due to the reaction between acid and base. As a result, it has a taste masking effect too[11]

Manufacturing process of this special kind of formulation is very critical, as we need a hightemperature & humidity controlled area to manufacture this formulation. Minimum temperatureof 20-25^{0}C and 20-25 % Relative Humidity is required to manufactureeffervescent formulation. A little change in procedure, formulation or packaging have a valuable influence on finished formulation [2, 12].

Though, determining the correct formula is very much important in any formulation in pharmaceutical field, their manufacturing in a proper way as per all guidelines by FDA for respective market or ICH is also very important. In the present article, we are going to discuss about the process and its criticality regarding various effervescent formulations.

PROCESS

The effervescent formulation is prepared by combination of different acid and base especially citric acid, tartaric acid, and sodium bicarbonate[13],If an acid and a base came in contact with water during manufacture then, reaction may occur. So, it is very important to keep the acid and the base separate at the time of manufacturing and area should be free from moisture.

The overall manufacturing process of effervescent formulation is basically divided into following steps like:

- Dosing of the ingredients
- Mixing/Granulation
- Lubricating
- Tableting
- Packaging

Manufacturing of effervescent formulation is usually done in a semi-continuous process [13].Granulation, acid base mixing andpre-drying are the critical steps which strongly influence the final formulationdevelopment. Lubrication of granules, and compression should be done appropriately for achieving a desired extent of effervescence[13].

Effervescent formulation contains at least one medicament, whose physiochemical parameter are in total three stages viz.pre-drying and drying stage. The stages of variation are as below:-

- The humidification of effervescent mixture
- The pre-drying of humidification mixture
- The final drying of granulation mixture [14]

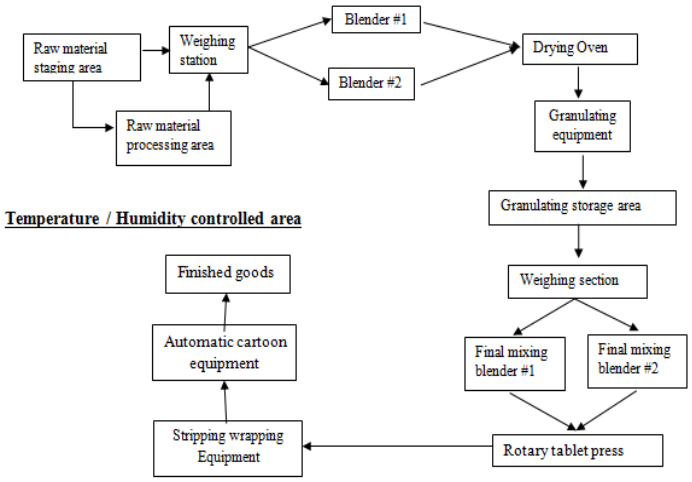

Fig: 1Manufacturing flow chart of Effervescent Formulation [13].

In the above flow chart, it has been suggested that two blenders should be used in manufacturing of effervescent formulation to maintain a continuous flow of material. If one batch is send to oven for drying, the other batch should be in the process of preparation. The time needed to prepare the granules should not be more than the time required for drying (if continuous low process have to be maintained). Some manufacturers weigh raw material outside the manufacturing area to avoid compounding error[13].

Various methods for manufacturing of effervescent formulation

Previous theories disclose that in a rapid dissolving effervescent tablet, the two reactants are separated by a layer of reacted product at the interface. The product requires a complex procedure involving the injection and extraction of a volatile organic solvent and results in a tablet that has 15-35% voids and would also not be suitable for the commercial distribution[15].

Many other patents were published regarding manufacturing of effervescent formulation which state that a liquid is carbonated in contact with aluminosilicate molecular sieves saturated with carbon dioxide. It has many disadvantages like it was bulky and expensive[16].

For drug likesLevetiracetam (antiepileptic drug), which has a short half-life of 6.5 hours, but it has to be administered at a high dose (500 mg) twice a daily, a suitable dosage form has to selected which is easy to administer but has a sustained release too. So sustained release micro-particles are prepared bysolvent.

Evaporation technique then the micro-particlesare made into effervescent granules[7].

TOPO granulation

Topo granulation is a modern granulation technique used and patented by HermasPharma in which surface modification (17) of the citric acid was done by applying a passivation to the surface of the mixture during granulation. The granulation process can be controlled by applying a vacuum during the procedure. Thus, an effervescent tablet, which is quickly and completely soluble and at the same timeextremely resistant to humidity, was produced.

TOPO granulation has a lot of benefits as compared to conventional granulation procedures like:-

- The product produced by TOPO granulation dissolves very quickly in water, as the release of carbon dioxide in water starts immediately.
- It is extremely moisture resistant which enables a long shelf life of the finished product
- Thus, increase its market value and its use in tropical regions; products for countries even in climatic zones IV+ can be supplied without difficulty.
- The citrate coating facilitates increased stability against acid-sensitive agents.
- Also alkaline agents can be coated; this benefit is equally effective for agents sensitive to alkali.
- Manufacturing can take place at a relative humidity of 30 %within the room.

The atmospheric pressure lowered by the vacuum leads to reduced drying temperatures and shorter drying times. Fill capacities ofabout 500 kg granulate can generally be dried within 15 minutes. In this granulation process, we can get a transparent solution of Paracetamoleffervescent tablet with equal distribution of API. As the flow characteristics is improved due to enlarged particle size, dosage accuracy and a homogenous distribution of the agent is achieved without additional blending, enabling more efficient manufacturing. The effervescent tablets disintegrate quickly, even if stored over a long period. The quick and transparent dissolution of the paracetamol is achieved by the addition of surface-active agents, as well as the above described granulation ofparacetamol with the effervescent components. Due to its excellent thermal stability, paracetamol can be granulated directly with the other components, without riskingchemical degradation of the API. Only small quantities of water wasadded and no organic solvent. The procedure is not hazardous to the environment.Large granule size increases flow properties as well as dose accuracy[9].

Evaluation of tablets

This is a very complicated process and should be done very carefully.

Tablet thickness / tablet diameter = 1

(If result more closely to one more the hardness of the tablet)

By this we can know the proper tablet hardness. Other processes like disintegration, friability are same as conventional process as per USP guidelines.

Table 1.Volume and temperature used in disintegration of effervescent tablets

Tablet	Water volume	Water temperature
Antacid/ Analgesic	120-180	15-20
Denture cleanser	120-150	40-45
Flavoured beverage	180-240	10-15
Mouthwash	20-30	25-25
Toilet bowl cleaner	4000-6000	20-25

Critical Effect of Binders and Lubricants

During manufacturing of effervescent tablets, some problem arises like,
Low compressibility
Large dimension of tablet
Poor binder addition

These problems result in Laminationand capping problem. This can be detected manually by pressing the tablet between fingers.Difficulty in addition of lubricating mixture is evident due to loss of shine in tablet surface. Problem with binder affects disintegration of tablets while problem in lubricants affects hardness of tablets. Choice of tablet press is also very important. Now-a-days some equipment manufacturer provide equipment's that are able to provide external lubrication to granules, i.e. anti-adherent material are directly sprayedto the dies at the pause phase of tablet compression, so that chances of sticking of raw material in the dies decreases[13].

Packaging problem

It states that acid and base is packed separately so that they cannot interact with each other and cause degradation during travelling or storage. This process was not accepted as all depends on the separator provided to separate acid and base component, because any damage to the separator could cause problems[20, 21].

Some patentsstate that effervescent tablet does not require any special packaging. Thus,inventually multi-layers tablets were invented[20].

Now-a-days, the most common type of packaging used are foil packets and tubes. Pinholes are a common problem in foil packets.It can be avoided by using heavier gauge foils which are more expensive then general foils[22].

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