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FORMULATION AND EVALUATION OF ORALLY DISINTEGRATING PELLETS

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ABSTRACT

The main aim of the present study was to evaluate the potential of orally disintegrating pellets (ODPs) as an approach for taste masking of Mebendazole using ion exchange resin. The drug resin complex was prepared in batch method with complexation of drug with resin. Maximum drug loading capacity of resins Kyron T-134 was calculated then Drug Resin Complexes were optimized by effect of drug resin ratio. Pellets were prepared by extrusion/spheronization with kyron T-134, Kyron T-314, sucrose, corn starch, sucralose, Vaniline flavor, and 1% PVP solution. The prepared pellets were characterized for percentage yield, drug content, particle size, in vitro drug release & in vitro disintegration. The obtained ODPs disintegrate in less than 20 s. So, conclusion, states that ODPs can be utilized as an alternative option for effective taste masking and rapid disintegration in the oral cavity.

KEYWORDS: Pellets, orally disintegrating, Kyron, Drug- resin complex.

INTRODUCTION

Pellets are granules or fine powder of bulk pharmaceuticals ingredients and excipients agglomerated together. They are primarily meant for oral delivery and are composed of small, free-flowing, spherical or semi-spherical solid units ranging in size from 0.5 mm to 1.5 mm.[1] Pellets are classified as a Multi-particulate Drug Delivery System and have several advantages over single unit dosage forms, including less susceptibility to dose dumping and food ingestion, which results in less variability in drug plasma absorption profile between subjects and within the same patient.[2,3] It can be split into the necessary dose strength without affecting the procedure or formulation.[4] Extrusion-spheronization is a well-

established method for producing medicinal pellets. Wet extrusion and hot melt extrusion are the two types of extrusion methods.[5]

When a medicinal product's flavour, aroma, and colour contribute to its acceptance, it has a good effect. Taste, smell, texture, and aftertaste are all essential considerations in the formulation of oral dose forms and the establishment of guidelines to manage paediatric patient compliance.[3] In terms of patient acceptability and compliance, flavour is one of the most important aspects influencing market penetration and financial success of oral formulations, particularly in paediatric medicine.[4]

The application of ODPs (drugs, taste masking agents, and superdisintegrants) as a method for flavour masking and rapid disintegration is innovative in this work. Ion exchange resins are solid, insolubilized polyelectrolytes has a high molecular weight that may reversibly and stochiometrically exchange mobile ions of equal charge with the surrounding medium. They come in the desired size ranges. Bitter cationic medicines can be adsorbed onto carboxylic acid's weak cation exchange resins to functionally produce a non-bitter complex. Furthermore, resinates can be made into lozenges, chewing gum, suspensions, or dispersible tablets to conceal the flavour.[6,7]

MATERIALS AND METHOD

Material: Mebendazole was received from Yarrow Chem Products, Mumbai, Kyron T-134 & Kyron T-314 was procured from Corel Pharma Chem, (Ahmedabad), Sucrose, Crospovidone, Vaniline, Citric acid were obtained from Research Lab Fine Chem Industries, Mumbai, Starch, Aspartame, Poly Vinyl Pyrollidone Ozone International. Deionized distilled water was used throughout the study.

Preparation of Drug: Resin Complex

Drug: resin (Kyron T-134) was taken in 1:1 ratio. An accurately weighed quantity of resin was taken in a 100 ml beaker containing 30 ml of deionised water. Resin was allowed to swell for 30 min. Appropriate amount of drug (as per 1:1 ratio) was added into the same beaker and pH of solution was recorded. The beaker was placed on an OSC India magnetic stirrer 900 rpm for 30 min at 30°. After the stirring procedure the solution was filtered using whatsman filter paper. The filtrate was analyzed using appropriate dilution for determination of unbound drug at 278.6 nm using Lab India UV spectrophotometer. The residue on filter paper was dried in a hot air oven at 40°-50°. Percentage of drug bound to resin was calculated.

Characterization of DRC

The optimization of drug loading capacity of resin was performed by determining the effect of various factors on drug loading. The below table shows % drug loading in DR complex.

Table No. 1: % Drug Loading in Drug-Resin Ratio.

Drug- Resin Ratio	% Drug Loading
1:1	55.08 %
1:2	88.06 %
1:3	91.416 %
1:4	91.224 %

Formulation Table and Method of Preparation

4 gm of drug-resin complex (contains 1 gm of drug) was weighed. Excipients like starch, sucrose, crospovidone, Kyron T-314, aspartame, vanilline and citric acid was added. All ingredients were mixed in a mortar properly. 250 mg of PVP was dissolved in 100 ml water (binder solution). The binder solution was further added slowly to converted into a cohesive mass. It was further passed through extrusion at 75 rpm and spheronize at 750-860 rpm for 4-5 min and the formed pellets were collected in a tray and dried in hot air oven at 40 ℃.

Ingredients	B1	B2	B3	B4	B5	B6	B7	B8	B9
DRC (gm)	4	4	4	4	4	4	4	4	4
Starch (gm)	6.950	6.450	5.950	6.450	5.950	5.450	5.950	5.450	4.950
Sucrose (gm)	2	2	2	2	2	2	2	2	2
Kyron T-314 (gm)	1	1	1	1.5	1.5	1.5	2	2	2
Crospovidone (gm)	1	1.5	2	1	1.5	2	1	1.5	2
Aspartame (mg)	25	25	25	25	25	25	25	25	25
Vanilline (mg)	10	10	10	10	10	10	10	10	10
Citric Acid (mg)	15	15	15	15	15	15	15	15	15
1 % PVP Sol^{n}	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total (gm)	15	15	15	15	15	15	15	15	15

Evaluation of Pellets

Micromeritic Properties

Angle of repose: Angle of repose is the maximum angle formed between the surface of pile of powder and horizontal plane. It is usually determined by fixed funnel method and is the ability to measure the flowability of powder

$$\theta = \tan^{-1} (h/r)$$

Bulk density: Weighed quantity of 10 gm pellets was transferred into a 100 ml measuring cylinder without tapping, during transfer the volume occupied by pellets was measured. Bulk

density was measured by using formula. Bulk density was calculated by using following formula,

$$\text{Bulk Density} = \text{Pi} = \frac{m}{Vo}$$

Where,

Pi = Bulk density

m = Mass of the pellets,

Vo = Untapped Volume

Tapped Density: Weighed quantity of 10 gm pellets was taken into graduated cylinder, volume occupied by granules was noted down. Then cylinder was subjected to 100 taps in tapped density tester (Electro Lab USP II), the % Volume variation was calculated by following formula.

$$\text{Tapped Density (Pt)} = \frac{m}{Vi}$$

Where,

Pt = Tapped density

m= Mass of the pellets,

Vi = Tapped volume

Carr's/compressibility index: based on bulk density and tapped density the percentage compressibility of tje pellets was determined by the following formula

$$\text{Carr's index (CI)} = \frac{Vi - Vo}{Vi} \times 100$$

Where,

CI = Compressibility index

Vo = Bulk density

Vi = Tapped density

Hausner´s ratio: It is measurement of frictional resistance of the drug. It was determined by the ratio of tapped density and bulk density.

$$\text{Hausner's ratio} = \frac{vi}{Vo}$$

Where,

Vo = Bulk density

Vi = Tapped density.

Particle Size Analysis: The pellets were then subjected sieving (Mechanical Sieve Shaker, Jayant Scientific, India) using a nest of standard sieves (4, 10, 20, 25, 40, 60) shaken for 10 min on a sieve shaker. The pellets retained on each sieve were used to construct frequency distribution.

Percentage yield

The yield was determined by weighing the pellets and then finding out the percentage yield with respect to the weight of the input materials. The formula for calculation of percentage yield is

$$\text{Percentage yield (\%)} = \frac{\text{Weight of pellets}}{\text{Weight of drug + Weight of polymers}} \times 100$$

In Vitro Disintegration Time: *The in vitro disintegration time was determined for the pellets. This test was performed to ensure disintegration of pellets in the salivary fluid. In vitro disintegration time was measured by dropping a little quantity of the pellets in a measuring cylinder containing 6 mL of simulated salivary fluid of pH 6.8. The disintegration time was defined as the time necessary for the ODPs to completely disintegrate until no solid residue remains or only a trace amount of soft residue remains.*

In Vitro Dissolution Studies*:* Dissolution studies werecarried out following the USP II paddle method at 37∘C and 100 rpm using a dissolution tester (Electrolab TDT-06PL Dissolution tester, Mumbai, India). The dissolution medium was 900 mL simulated saliva fluid without enzymes (SSF) at pH =6.8. The amount of ODPs used was equivalent to 100 mg of Mebendazole. At specified time intervals (5, 10, 15, 20, 30, 40, 50 and 60 mins), samples were withdrawn, and assayed simultaneously for drug content spectrophotometrically 278.6 nm against blank after appropriate dilution.

RESULT AND DISCUSSION

Drug Loading: It was found that, the drug loading efficiency of resin increases as the resin concentration increases, as shown in Table 1. Percentage of drug bound to resin was found to be more when drug: resin was taken in the ratio of 1:3; since a marginal increase in percentage of drug bound to resin was observed from 1.1 to 1.3 ratio; the 1:3 ratio was selected for further study. In above table the DRC ratio 1:3 (1 gm drug & 3 gm kyron T-134) shows the highest drug loading as compare to other DRC ratio that is 91.416 %.

Particle size and drug content: Particle size analysis was determined by using Sieve Analysis method. In general, the volume weight mean of the manufactured pellets was found to be in range from 0.5 to 1.2 mm. The results had shown that particle size ranges between 0.67 to 0.75 mm.

Drug content of all batches was found in between 93-98 %. From the among batches B5 shows highest drug content that was 98.5 %. Indicating the uniformity in drug content.

Micromeritic study: The angle of repose was determined on prepared pellets. Angle of repose of batches is between 23-26. All the batches shows good angle of repose. The angle of repose of granules for optimized batch is 23.08.

The bulk density of all the batches ranges from 0.54-0.62 & tapped density is in between 0.61-0.74. The bulk density for optimized batch B5 was found to be 0.5570 gm/ml and tapped density was 0.619 gm/ml.

The carr's shows good flow property. For B5 Carr's index was 10.0, Hausner's ratio was 1.11. All the parameters lies within the specified range. The flow properties of pellets were good as compared to that of flow properties of pure drug.

Percent Yield, Friability and In vitro Disintegration Time: The percentage yield of pellets determined by weighing after drying the maximum percentage yield were found of F4 and F5 batches were noted be 91.06% and 93.24 %. Average percentage yield of spherules was greater than 81 % for all batches. Percent friability of all batches was found in between 0.3-0.9, It shows that all batches have good mechanical strength.

In vitro Disintegration test was carried out in phosphate buffer of 6.8 pH. Disintegration time of all batches was found in between 15-25 sec.

In vitro Drug Release: The in vitro cumulative drug release profile of these formulations showed up to 94.14 % release in 60 min. The formulation B5 showed satisfactory drug release in 60 min i.e. 94.14% which is considered as an optimized batch. During the study it was concluded that the pellets were dissolves speedly and gaves highest percent drug release. The percentage of both super disintegrants (Kyron T314 & Crospovidone) 10% of each gives fast and high drug release as compare to other formulations.

CONCLUSION

In the present study, an attempt was made to mask the taste of Mebendazole by using Kyron T-134 as an ion exchange resin was succesful. Various parameters affecting taste masking, such as resin ratio, pH, temp, soaking time of resin, and stirring time were optimized with efficient loading of drug. The nature of the DRC is such that the average pH of 6.8 in saliva is not able to break the complex, the DRC is weak enough to be broken down at gastric pH 1.2, thus the complex is considered absolutely tasteless in salivary fluid. In future, the orally disintegrating solid dosage forms may be most acceptable and prescribed dosage form due to its quick action. Thus, the "patient-friendly dosage form" of the bitter drugs, especially for paediatric, geriatric, bedridden and non co-operative patients was successfully developed using these technologies.

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