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FORMULATON AND EVALUATION OF BILAYERED TABLETS OF METHOCARBAMOL AND ACETAMINOPHEN

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ABSTRACT

Oral route is the most convenient and commonly used method of drug delivery. More than 50% of drug delivery systems available in the market are oral drug delivery systems. They offer convenience and ease of administration, greater flexibility in dosage form design and ease of production and low cost. Pharmaceutical oral solid dosage forms have been used widely for decades mainly due to their convenience of administration and their suitability for delivery of drugs for systemic effects. The most commonly used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules. Tablet delivery system can range from simple immediate release formulations to complex extended or modified release dosage forms. The most important role of drug delivery system is to get the drug delivered to the site of action in sufficient amount & at the appropriate rate. However it should meet other important criteria such as physical & chemical stability, ability to be mass-produced in a manner that assures content uniformity.

KEYWORDS: Oral route, granules, pellets, tablets, capsules, tablet delivery system, oral solid dosage forms.

INTRODUCTION

Solid dosage forms are widely prevalent due to their age-old application. Especially, oral solid formulations hold a high potential as they serve to be most convenient for the administration of drugs. These have been developed into a wide range of formulations from conventional dosage forms for immediate release of the drug to controlled release dosage forms for the constant rate of drug release. Oral rouse is the most convenient and commonly

used method of drug delivery. More than 50% of drug delivery systems available in the market are oral drug delivery systems. They offer convenience and ease of administration, greater flexibility in dosage form design and ease of production and low cost. Pharmaceutical oral solid dosage forms have been used widely for decades mainly due to their convenience of administration and their suitability for delivery of drugs for systemic effects. The most commonly used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules.

Tablet delivery system can range from simple immediate release formulations to complex extended or modified release dosage forms. The most important role of drug delivery system is to get the drug delivered to the site of action in sufficient amount & at the appropriate rate. However it should meet other important criteria such as physical & chemical stability, ability to be mass-produced in a manner that assures content uniformity.

Advantages

- Offers greatest capability of all oral dosage forms for the greatest dosage precision &
- Least content Uniformity.
- High patient compliance.
- Their cost is lowest of all dosage forms.
- Easiest and cheapest to packaging and shipment.
- They are having best combined properties of chemical, mechanical and microbiological properties.

Disadvantages

- Some drugs resist compression owing to their amorphous nature & low density character.
- Drugs with poor wetting, slow dissolution property, large dosages or any combination of these features may be difficult or impossible to formulate & manufacture as a tablet.

Types and Classes of Tablets

- Tablets are classified by their route of administration or function, by the type of drug delivery system they represent within that route, by their form and method of manufacture.
- Tablets ingested orally

1. Compressed tablets (CT)

2. Multiple compressed tablets (MCT)

a. Layered tablets – Bi-layer tablets

b. Compression coated tablets

3. Repeat action tablets
4. Delayed action and enteric coated tablets
5. Sugar and chocolate coated tablets
6. Film coated tablets
7. Air suspension coated tablets
8. Chewable tablets

Tablets used in oral cavity

1. Buccal tablets
2. Sublingual tablets
3. Troches, Lozenges and dental cones

Tablets used to prepare solution

1. Effervescent tablets
2. Dispensing tablets (DT)
3. Hypodermic tablets (HT)
4. Tablet triturates (TT)

HPLC Chromatogram of Acetaminophen and Methocarbamol Bilayer Tablet

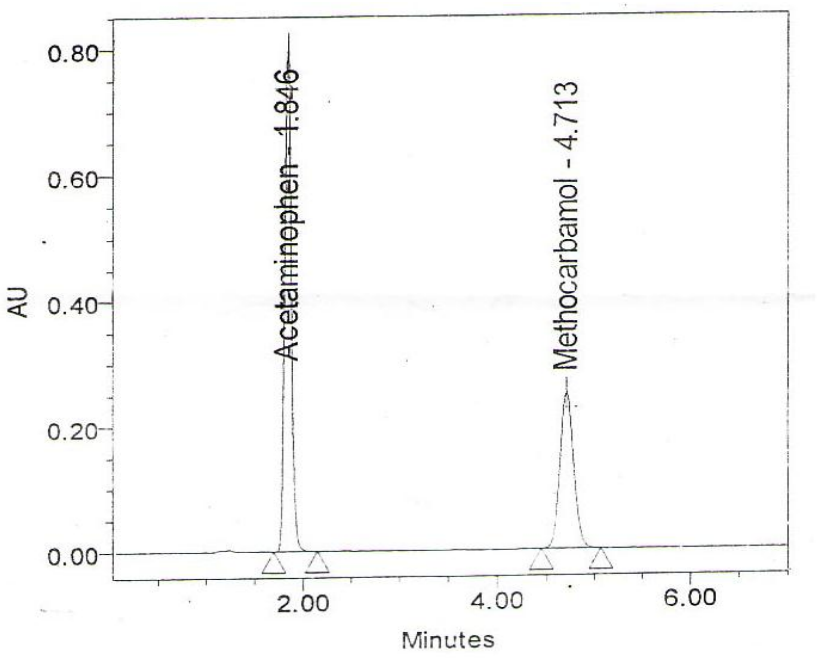


Table no 1: Parameters of uncoated tablet.

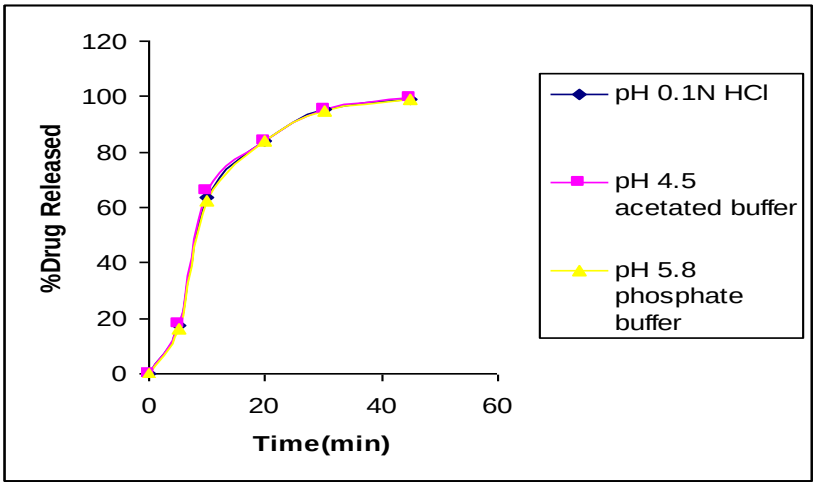
S.No	Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Average weight of tablets-gm	892.1	889.9	893.4	890.4	892.6	889.6	851.8	853.6	854.7	852.9	850.9	855.1
2	Thickness –mm	6.53-6.58	6.43-6.51	6.39-6.54	6.47-6.59	6.42-6.53	6.51-6.56	6.41-6.53	6.42-6.51	6.40-6.49	6.43-6.50	6.50-6.57	6.50-6.53
3	Hardness Kp	17.2-24.2	12.7-14.9	11.3-14.4	14.7-21.5	13.5-20.8	15.2-20.5	12.9-16.3	14.6-17.5	14.1-17.1	14.3-16.4	11.6-13.7	11.6-14.5
4	Disintegration time-min.sec.	30.0	8.37	6.55	7.00	6.00	10.30	4.32	5.25	6.40	3.30	5.10	3.30
5	Friability %	0	0.20	0.21	0.19	0.12	0.05	0.19	0.14	0.10	0.10	0.14	0.16

Comparative dissolution study of innovator product in different media

A) Comparative In-Vitro dissolution study of innovator product in different media

METHOCARBAMOL

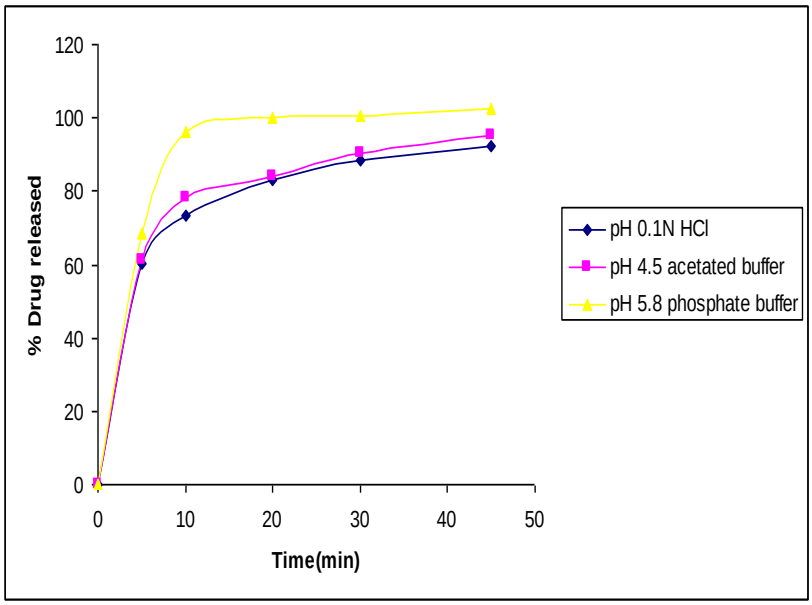
Time in min	pH 0.1N HCl	pH 4.5 acetated buffer	pH 5.8 phosphate buffer
5	17.1	18.2	16.4
10	63.4	65.7	62.5
20	84.1	84.3	83.9
30	95.2	95.5	94.9
45	99.1	99.7	99.2



Graphical representation of Comparative In-Vitro dissolution study of Methocarbamol layer of innovator product in different media

ACETAMINOPHEN

Time in min	pH 0.1N HCl	pH 4.5 acetated buffer	pH 5.8 phosphate buffer
5	60.2	61.4	68.7
10	73.6	78.2	96.2
20	83.1	84.2	99.9
30	88.2	90.6	100.4
45	92.3	95.1	102.3



EVALUATION TESTS

1. Tablet size and thickness

Graphical representation of Comparative In-Vitro dissolution study of Acetaminophen layer of innovator product in different media.

EVALUATION TESTS

1. General appearance

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by Vernier Calipers scale. The thickness of the tablet related to the tablet hardness and can be used an initial control parameter. Tablet thickness should be controlled within a ±5%. In addition thickness must be controlled to facilitate packaging.

2. Average weight of Tablets

Take randomly 20 tablets and weigh accurately 20 tablets and calculate the average weight.

$$\text{Average weight} = \frac{\text{Weight of 20 tablets}}{20}$$

3. Weight variation test

It is desirable that all the tablets of a particular batch should be uniform in weight. If any weight variation is there, that should fall within the prescribed limits:

±10% for tablets weighing 130mg or less

±7.5% for tablets weighing 130mg-324mg

±5% for tablets weighing more than 324mg

The test is considered correct if not more than two tablets fall outside this range. If 20 tablets are taken for the test and not more than 1 tablet fall outside this range if only 10 tablets are taken for the test. The difference of weight in tablets can lead to variation in doses. For carrying out this test 20 tablets at random are taken and weighed. The weights of individual tablets are then compared to equal to average weight.

4. Friability

This test is performed to evaluate the ability to withstand abrasion in packing, handling and transporting. Initial weight of 20 tablets is taken and these are placed in the friabilator, rotating at 25rpm for 4min. the difference in the weight is noted and expressed as %. It should be preferably between o.5 to 1.0%.

5. Hardness test

This is to force required to break a tablet in diametric compression. Hard ness of the tablet is determined by Stock's Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moving along the gauze in the barrel which the tablet fractures. Hardness of 5 kg considered as suitable for handing the tablet.

6. Moisture content by K.F.

Take a suitable quantity of anhydrous methanol in the titration flask, and titrate with Karl Fisher reagent to the end point. Grind ten tablets to fine powder in a dry mortar, weigh accurately between 0.2 to 0.5 g of the powdered sample, transfer quickly to the titration flask, and dissolve by stirring and titrate with Karl Fischer reagent to the end point.

CALCULATION

$$\text{Water \%} = \frac{V \times F \times 100}{\text{Weight of sample in mg.}}$$

Where,

F = Factor of Karl Fischer reagent consumed for sample preparation.

V = Volume in ml of Karl Fischer reagent consumed for sample titration.

7. Uniformity of dosage units (by weight variation method)

Take randomly 30 tablets, weigh collectively and individually 30 tablets and calculate average weight of the tablets and % assay of individual dosage units by using formula

$$= \frac{\text{Assay} \times \text{Individual weight}}{\text{Average weight}}$$

8. Disintegration Time

Place one tablet each in six tubes of the basket. Suspend the assembly in water maintained at a temperature of 37 ^{o}C ± 2 ^{o}C and operate the apparatus. Simultaneously, start the stopwatch, observe the tablets. Stop the stopwatch when the last tablet gets disintegrated. The tablets pass the test, if all tablets have disintegrate completely, repeat the test on 12 additional tablets; not less than 16 of the total of 18 tablets tested disintegrate completely.

SUMMARY AND CONCLUSION

The study was undertaken with an aim to formulate combination of pain reliefing agents as bilayer tablets. The literature shows that Methocarbamol is a skeletal muscle relaxant which acting centrally through inhibiting inter neuronal activity and blocking polysynaptic reflex pathway at spinal cord and at descending reticular formation at brain. Due to this reason it is used mainly in the treatment of chronic low back pain. Acetaminophen is thought to act primarily in the CNS, increasing the pain threshold by inhibiting both isoforms of cyclooxygenase, COX-1 and COX-2, enzymes involved in prostaglandin (PG) synthesis, which is responsible for pain sensation. At the present efforts are directed towards the formulation development of bilayer dosage form for the pain reliefing drugs.

During the phase of investigation various factor likely to affect the performance of the bilayer apparatus are felt necessary to be discussed in light of sound theoretical knowledge. Dissolution rate, intrinsic solubility, particle size of the drug, hardness, thickness, friability found to be critical during granulation are some of the factors found to be critical during the development based on the experimental findings. In the present study, SLS was found to play a great role in enhancing the dissolution of the Methocarbamol layer. In the study high

percentage of drugs in the granulation were cost effective and as well as cause of requiring less compression force which is very important for the bi layer technology.

With the data from literature review, Preformulation study prototype formulation was started, placing Acetaminophen layer on precompressed Methocarbamol blend optimized layer. For both layer wet granulation process was used for the formulation, where Methocarbamol layer in RMG process and Acetaminophen layer in FBP process.

Granules were evaluated for test such as LOD, Bulk density, Tapped density, Compressibility index, Hausner ratio and sieve analysis before being punched as a tablet. The prepared tablets were then tested for weight variation, thickness, hardness and friability. In-vitro dissolution tests were performed and F10 values were calculated. Dissolution profile was found to match with the Innovator product and F10 value was found to be satisfactory. From the above study results, it can be conclude that F10 formulation showed the desire results and was found to be suitable for large scale production. Two reproducible batch were done, process parameter and results were found similar with the optimized formulation. The stability study of the final formulation for 3 months shows that the formulation is stable enough at 25 ºC/ 60%RH and 40^0C/75% RH. Accordingly, it can be concluded that the final formulation is a robust one and the performance is less likely to effected by the various factors study. An excellent in vitro-in vivo correlation is expected as evidence from degree of similarity found in dissolution study.

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