



FORMULATION AND EVALUTATION OF DUAL RELEASE MULTIPLE UNIT TABLET FORMULATION

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ABSTRACT

Formulations studies were conducted to ascertain the feasibility of designing a multiple-unit tablet formulation containing two drugs with different release characteristic. The objective of the study was to employ hydrophilic gums that swell rapidly in the design of controlled-release drug pellets. Controlled-release pellets of pseudoephedrine hydrochloride were prepared by powder layering blend of drug with hydrophilic gums-guar and xanthan gum mixture in ratio 8:2, on to nonpareil seeds. The pellets were subsequently film-coated with HPMC to facilitate their free dispersion after disintegration of multiple-unit tablets in aqueous media. Controlled-release film coated-pseudoephedrine pellets were then compressed along with directly compressible cushioning excipients-microcrystalline cellulose and lactose and the other drug loratidine in to multiple-unit tablets, which were subsequently film-coated with. Evaluation of the compressed

multiple- unit tablet formulation revealed that the tablets had a good mechanical strength and show rapid disintegration. In vitro disolutation studies on controlled-release pseudoephedrine pallets and multiple unit tablets demonstrated that the release of pseudoephedrine from multiple unit tablet formulation was retarded as compared to release from intact pellets. The immediate release characteristic of loratidine remained unaltered.

Key Words: Multiple-unit; Pellets, Pseudoephedrine hydrochloride and loratidine, Hydrophilic gum, controlled release.

INTRODUCTION

It is recognized that a multiple unit controlled release dosage form present a better alternatives to a single unit system for oral administration^[1]. An ideal multiple unit tablet dosage form is the one, which on oral administration, disperse or disintegrate readily in stomach to release a large number of drug particle, granules or spheroids that have maintained the integrity of both the cores, and their release- retarding properties such that their drug release kinetics are unaltered^[2]. As a multiparticulate dosage form, controlled release drug particle are normally filled in to capsules. However, it is not easy to present a low potency, high dose drug in the form of multiparticulate drug delivery system. This is mainly due to large size of hard gelatin capsule shell required for such dosage, which may be difficult to swallow, leading to patient compliance problem. Compaction of controlled release drug particle is an alternative to capsule formulation. Is shown in fig. 1.

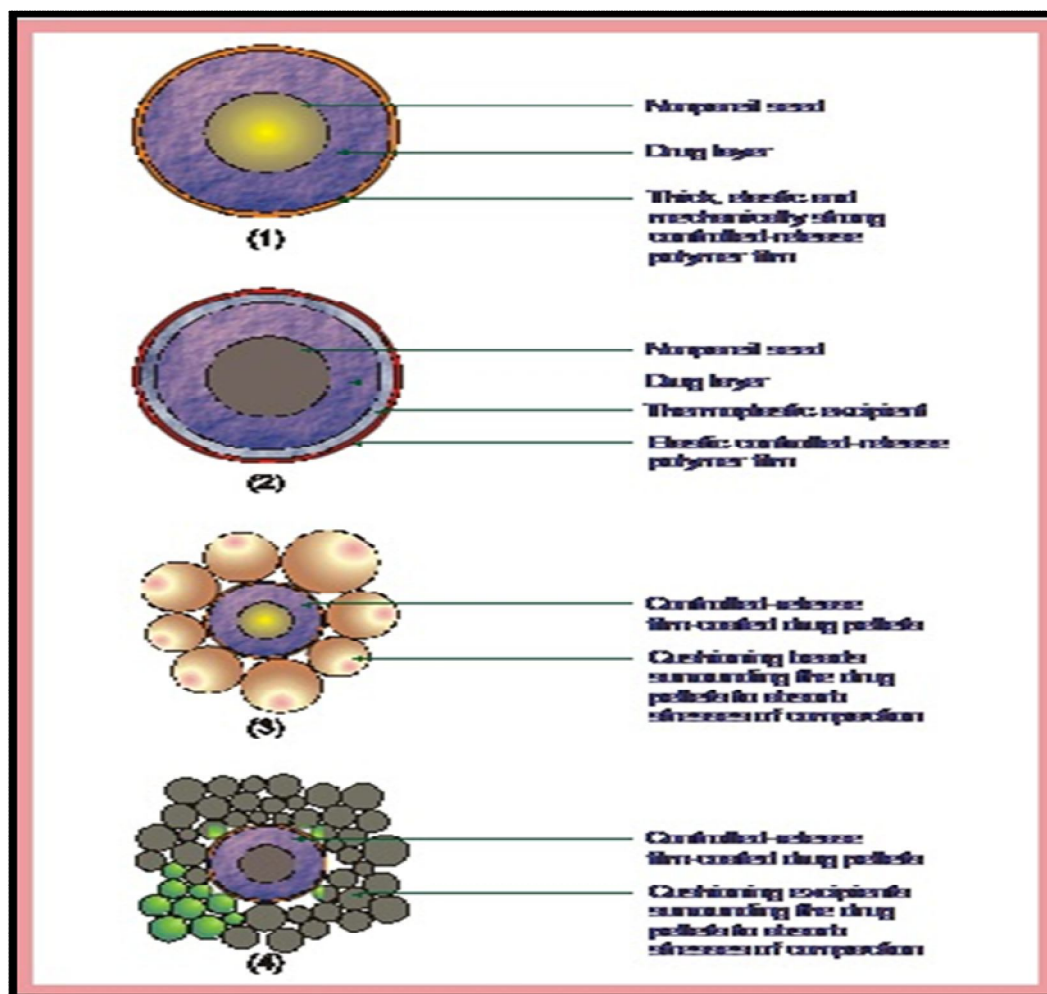


Figure 1. Schematic representation of the various approaches to prepare multiple –unit controlled release tablet formulation.

ADVANTAGES

1. The preparation is swallowed easily because the unit is smaller in size, Production cost is very low.
2. Ability to administer a portion (dose division) of such multiple unit tablets without compromising their controlled release properties, ability to incorporate larger dose of drug in controlled release form is comparison to capsule.
3. Ability to formulates such tablet in a dispersible base that can be reconstitute during the use to form suspension that can be easily swallowed and hence suitable for children and elderly.^[5]
4. Sustained delivery of large doses of biologically active ingredients is also possible in this way and it is advantageous in comparison to tablet and capsule, which owing to their size will be difficult to swallowed and in comparison to chewable tablets where chewing would result in loss of controlled release characteristics, Better stability of the products under ambient condition owing to its compact nature.

Approaches of a multiple unit tablet dosage form of controlled release spheroids

1. Application of a coat of thermoplastic excipients such as waxes on the drug core that will deform plastically during a compression step and thus absorb the stresses that may otherwise tear or fissure the outermost surface coating.^[9]
2. Imparting suitable mechanical properties to the polymer film on the drug spheroids in Order that they can withstand the compaction process with minimal damage to the integrity of coating^[6-8]. This approach generally involves either increasing the flexibility of the coat or increasing the amount of coating applied.
3. Use of cushioning beads or placebo pellets as excipient which are mechanically weaker than the coated controlled release drug spheroids to form tablets such that during compaction, the placebo pellets preferably undergo fragmentation rather than plastic deformation while preventing damage to drug pellets.^[3-4]
4. Use of dry powder of certain materials as external excipients to provide cushioning effect during compaction cycle.^[10]

MATERIAL AND METHOD

Material

Model drug- Pseudoephedrine hydrochloride and Loratidine.

Pseudoephedrine hydrochloride, is a nasal decongestant with a short plasma half life of about

5-8 hours which is freely water soluble (and hygroscopic) was as chosen as the drug candidate for making controlled- release spheroids. Design of controlled-release system of freely water soluble drugs poses a big challenge in a way that relatively large amount of release retarding agent is required to control the release rate of such drug. This drug is thus a good candidate for the present study. Loratidine, a non- sedating histamine H1 receptor antagonist with antiallergic properties and long half life was chosen as the immediate release component in the present formulations. The dosage form was designed to contain 120 mg pseudoephedrine hydrochloride and 5 mg loratidine for twice daily dosing and both the drug were obtain from Zim Laboratories Ltd. Kalmeshwar, Nagpur (India).

Hydrophilic gum

Hydrophilic polymers ^[13] blends that swell rapidly were employed in the present study. Gaur gum: Xanthum gum mixture in the ratio 8:2 was used since this blend in the stated ratio is known to demonstrate rapid swelling as well as remarkable viscosity synergism ^[11]. This fact was confirmed by preliminary interaction studies between the two polymers ^[14]. The hydrophilic gums used a had a loss on drying (LOD) value of less than 3%. Both the hydrophilic gums were also obtained from Zim Laboratories Ltd.

Other excipients

Other excipients used in the present study can be divided in top two categories.

1. Those that were employed for making controlled release drug pellets, and
2. Those that used to make multiple unit tablets.

Adjutants used for making the controlled release drug pellets of pseudoephedrine hydrochloride were nonpareil seeds (30-40 mesh) as the substrate for drug layering, purified talc as the anti tack agent during dry powder layering, lactose as the diluents and PVP K 30 as the binding agent. Since the drug is hygroscopic and required protection from moisture, film coating of pellets was necessary. Film coating composition included hydroxypropyl methylcellulose (HPMC) 5 cps. Additives employed to prepared the multiple unit tablets of pseudoephedrine hydrochloride (controlled release form) and loratidine (immediate release form) included spray-dried microcrystalline cellulose and spray-dried lactose as fillers having a good flow and compressibility sodium starch glycolate as the disintegrate, colloidal silica as the glidant and disinter\grants and purified talc and magnesium stearate as lubricant, glidant and antiadherent. The compresses tablets were given a final film coating to further protect the hygroscopic drug pseudoephedrine hydrochloride. Tablets film coating composition included

hydroxypropyl methylcellulose (HPMC) 5 caps as the film former, polyethylene glycol 6000 as the polishing agent, purified talc as the anti-tack agent, titanium dioxide as the opacifier and sunset yellow lake as the coloring pigment. All these excipients were of pharmacopeias grade and procured from Zim Laboratories Ltd.

METHOD

Design of multiple unit tablet formulation of pseudoephedrine hydrochloride and loratidine involve in two steps.

A. Pseudoephedrine hydrochloride controlled release pellet formulation design and composition.

B. Preparation of multiple unit tablets

A. Pseudoephedrine hydrochloride controlled release pellet formulation design and composition

Controlled-release pellets of pseudoephedrine hydrochloride were prepared by dry powder layering onto nonpareil seeds. Two approaches could be employed- layering the drug first on to the nonpareil seeds followed by depositing the hydrophilic gum layer or mixing the drug with hydrophilic gum layering the mixture on the neutral pellets. The latter technique was employed as it involved less number of processing steps and relatively easy to process. The formulation was so designed that the pellets release not less than 70% of the drug in 6 hours (suitable for b.i.d. dosing) two formulation A and B were designed containing different levels of synergy hydrophilic gum blend. About 120 mg pseudoephedrine hydrochloride was contained in approximately 370 mg of the final pellet formulation. Details of the pseudoephedrine hydrochloride pellets formulation as well its multiple unit tablets in combination with loratidine prepared in the present study are indicated in table 1. It is important to mention at this juncture that the HPMC film coating applied on the controlled release pellets of pseudoephedrine hydrochloride serves two purposes.

1. As a moisture barrier to improve the stability of the hygroscopic drug pseudoephedrine hydrochloride, and
2. After compaction, on exposure to dissolution environment, allow the tablet to disintegrate first in to controlled release pellets of pseudoephedrine hydrochloride. (Particle of immediate release of lorastidine) before they swell. Absence of such a film coating may lead to premature swelling of the tablet and impaired release characteristic of both the drug thus the HPMC film coat on the controlled release pseudoephedrine hydrochloride pellets acts as both

the protective film as well as the separating layer. Pseudoephedrine hydrochloride controlled release and loratidine immediate release multiple unit tablet formulation design and composition. In the development of multiple unit tablet containing controlled release drug the major challenges is preventing the undesirable effects of compaction on the biologically active ingredients release. With regards to the formulation under study, where swellable polymers matrix controls the drug release and not the polymer membrane coating, the criteria important is not the type and amount of coating on the controlled release pellets but the selection of external additives that are directly compressible and have cushioning effects and the magnitude of pressure applied cushioning additives are those which prevent the controlled release drug pellets from getting damage both morphological and in terms of release characteristic, after compaction. Since the object was not to prevent damage to film coating on the pellet, the formulation was further simplified by making use of optimized diluents blend of simple cushioning excipient viz Spray dried microcrystalline cellulose and spray dried lactose in ratio 1:1 as proposed by ^[10]. Aulton also proposed that the minimum amount of filler excipients required to fill efficiently the void space between the pellets is 40% of the total tablets composition and hence this amount of cellulose lactose blend was used in the present study while designing the multiple unit tablet formulation. To further make the preparation less complicated, loratidine was admixed with filler excipient instead of incorporating the same in the film coating applied on the tablet after compaction and idea contrary to patented formulation of pseudoephedrine and loratidine ^[12] is shown in the following table 1.

Table 1. Multiple tablets formulation A and B of pseudoephedrine Hydrochloride and Loratidine

INGREDIENT	Quantity (Mg/tablet)	
	Formulation A	Formulation B
1.Preparation of controlled release pseudoephedrine hydrochloride pellets		
A. Core Material		
Nonpareil seeds (30/40)	60	60
B. Drug and hydrophilic gum layer		
Pseudoephedrine HCL (200Mesh)	120	120
Guar Gum (200 mesh)	80	96
Xanthum Gum (200 mesh)	20	24

Lactose	20	-
Purified talc (200 mesh)	40	40
PVP K-30	10 approx	10 approx
C. Film Coating (moisture barrier and separating layer)		
HPMC 5 caps	20	20
Total weight (Film coated pellets)	370	370
2. Preparation of multiple unit tablets of pseudoephedrine hydrochloride and loratidine.		
A. Core Tablets		
Film Coated pseudoephedrine SR pellets (Form 1)	370	370
Loratidine (200 Mesh)	5	5
Lactose	130	130
Microcrystalline cellulose	130	130
Sodium starch glycolate	15	15
Purified talc	7	7
Magnesium stearate	3	3
B. Film Coating		
Magnesium Stearate	3	3
HPMS 5 caps	7.5	7.5
PEG 6000	1.5	1.5
Purified Talc	1.5	1.5
Titanium dioxide	2.25	2.25
Sunset yellow lake	2.25	2.25

B. Preparation of multiple unit tablets

The process of preparation of multiple unit tablet formulation containing controlled release pseudoephedrine hydrochloride and immediate release loratidine can be divided in to 2 stages.

1. Preparation of film coated controlled release pellets of pseudoephedrine hydrochloride and

2. Compaction of pseudoephedrine pellets and loratidine along with excipient into multiple unit tablets and their subsequent film coating.

Drug pellets of batch size containing 120 g of pseudoephedrine hydrochloride were prepared (approximately 370 g pellets were obtained after film coating). Pellets were prepared by powder layering technique in a 30cm diameter coating pan equipped with 4 radially arranged baffles. Drug, guar and xanthum gum and talc (all previously sifted through 200 meshes) were mixed together in the double cone blender for 15 minutes. Binder solution consisting of 5% PVP K-30 in isopropyl alcohol was continuously sprayed onto the cascading nonpareil seeds in the coating pan using a peristaltic pump and pneumatic spray gun. Drug and hydrophilic gum powder mixture was layered on to the wet and tacky nonpareils at regular intervals. After the completion of drug layering, the pellets were dried at 45°C in a tray dryer for 6 hours following which sifting was done to collect 16-20 mesh pellet fraction for film coating. Film coating was also carried out in the same coating pan with an organic solution of HPMC 5 caps (5% solution in 1:1 isopropyl alcohol-methylene chloride mixture) until an approximately 6% weight gain was achieved. Coated pellets were dried at 45°C in a tray dryer for 6 hours and sifted to collect 16-20 mesh fractions. Direct compression technique was adopted for preparing the multiple unit tablets. Batch size of the formulation was 500 tablets. The procedure involves sifting the directly compressible excipients—spray dried microcrystalline cellulose and spray dried lactose through 20 meshes, sifting the drug loratidine through 200 mesh, mixing pseudoephedrine hydrochloride pellets, microcrystalline cellulose, lactose, loratidine and sodium starch glycolate together in a double cone blender for 10 minutes, blending the latter mixture with purified talc and magnesium stearate for a further 5 minutes and compaction of the blend so obtained into multiple unit tablets using a single station tablet compression machine. The tablets so produced have the following specifications: average weight 660mg, hardness 4-5kg, diameter 13.2mm, thickness approximately 5.2-5.3 mm and disintegration time less than 3 minutes. Film coating of the multiple unit tablets was also carried out in the coating pan (see table 1 for formulation details). Aqueous film coating formulation containing HPMC was employed for coating of tablets. HPMC was first dispersed in purified water under stirred conditions. PEG was first melted separately and then incorporated in the polymer solution with stirring. Talc, titanium dioxide and sunset yellow lake were first blended and sifted through a 200 mesh screen followed by addition of the mixture to the polymer solution under stirred conditions. The polymer dispersion was further stirred for an additional 10 minutes to obtain a smooth and

homogenous coating composition. Before coating, the dispersion was passed through a 100 mesh nylon cloth. Solid content of the coating dispersion was 20%. The procedure adopted for film coating involved gradual spraying of coating dispersion on the dedusted tablets using a pneumatic spray system with hot air (60°C) and exhaust system on. Film coating was continued until the weight of tablets increase by approximately 5%. The film coated tablets so prepared had fooling specification average weight 675 mg and diameter approximately 13.6 mm, thickness approximately 5.5 mm and disintegration time less than 6 minutes.

Evaluation of controlled release drug pellets and multiple unit tablets.

Film coating pseudoephedrine pellets were evaluated for drug release profile. The multiple unit tablets were evaluated for following parameters- crushing strength, friability (of uncoated tablet) disintegration test, photomicrography and *in vitro* dissolution. The diametrical crushing strength of tablets was determined using Monsanto tablet hardness tester. Friability of tablets was evaluated by subjecting them a 100 revolution in a Roche friabilator (Electrolab) Magnified photographs of film coated tablet and fractured tablet were taken using intelplay digital microscope QX3 attach to a personal computer. The photograph was used to examine the extent of deformation of pellets at the tablet surface as well as within its core. Disintegration test (with out disc) was carried out according to the method described in USP 25 on both uncoated as well film coated tablet to determined how rapidly the tablet break open on contact with aqueous media water at a room temperature was used as the media for testing. *In vitro dissolution* testing of controlled release pellets and multiple unit tablets. In vitro release of pseudoephedrine hydrochloride was performed on film coated pellets as well as multiple unit tablets whereas dissolution for loratidine was carried out on the final multiple unit formulation to evaluate the dual release characteristic of the designed formulation. Dissolution condition for *in vitro* release of pseudoephedrine and loratidine are indicated in table 2.

Table 2. Dissolution condition for pseudoephedrine Hydrochloride and loratidine

	Pseudoephedrine	Loratidine
Dissolution Apparatus	USP 24 Apparatus 1	USP 24 Apparatus 2
Speed of rotation	100 rpm	100 rpm
Temperature	37°C ±0.5°C	37°C ±0.5°C
Sampling time	1,2,4 and 6 hours	1 hours.
Test medium	Water	0.1 M HCL containing 0.11% lauryl sulphate
Volume of test medium	900 ml in each vessel	1000 ml in each vessel

While performing the dissolution test on pseudoephedrine pellets, spheroid equivalents to 120mg drug (approx 370 mg pellets) were subjected to evaluation of release profile. Six samples of each formulation were tested. Ten (10 ml) aliquots were withdrawn from the dissolution vessels at stated interval. While carrying out dissolution of pseudoephedrine after withdrawal of sample an equal volume of dissolution medium was replaced. The amount of pseudoephedrine and loratidine dissolved were determined by HPLC (Shimadzu) equipped with L1 column (Shadon.250mm X 46 mm, 5 μ M), UV detector, P100. Isocratic pump and SP 4600 integrator. Pseudoephedrine was determined at 214 nm. While loratidine at 247 nm. Mobile phase for the former drug was filtered and degassed mixture of alcohol and 0.4% ammonium acetate solution (17:3) while for loratidine it was prepared by dissolving 80 mg of octane sulfonic acid sodium salt in a mixture of 200 ml water and 325 ml acetonitrile followed by addition of 0.3 ml of glacial acetic acid and adjustment of pH to 6.0 with triethylamine.

RESULT AND DISCUSSION

The possibility of preparing multiple unit tablets containing two drugs with different release characteristic viz. controlled release Pseudoephedrine and immediate release was practically evaluated in this study. Satisfactory tablets having good mechanical strength were produced with both the formulation A and B.

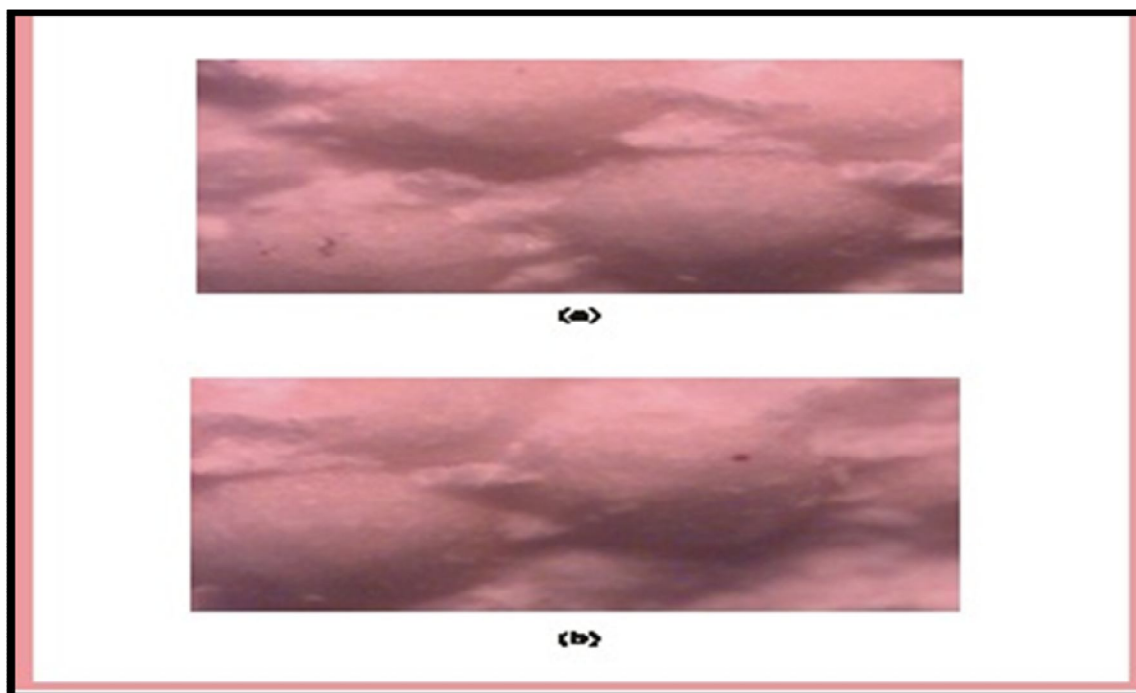


Figure 2. Stereo microscopy graphs of fractured surface (core) of multiple unit tablet formulation (a) and (b) showing the deform pellets magnification power (60).

Tablets properties of both formulations were comparable (see figure no. 3) Tablets of both the formulation had good mechanical strength as evaluated on the basis of the hardness and friability values. Disintegration of both uncoated and film coated tablets was fast enough to facilitate separation of controlled release Pseudoephedrine hydrochloride pellets as discrete unit that an release the drug in sustained manner independently a characteristic expected from such a multiple unit compacted system. Moreover, proper disintegration also facilities rapid release of loratidine, the other drug meant for demonstrating immediate therapeutic effects. The extent of deformation of pellets on the tablets surface and within its core was observed with optical microscopy. Fig. 2a and 2b.

Depict the film coated pseudoephedrine pellets before and after compaction. Fig. 2b. Shows that the extent of deformation of pellets within the fractured tablet. As evident from the figure and as anticipated, pellets were largely deformed on tablet surface owing to the impact of punch faces and die. Degree of deformation was much less within the tablet core since the cushioning excipients acted as the buffers against the compression pressure. Appearance of deformed drug pellets on the tablets surface and within the fractured tablets core indicates that they had undergoes plastic deformation and fragmentations were virtually absent. This feature was thus responsible for separation on intact, although deformed, drug pellets on disintegration. Much of this characteristic can also be owed to the presence of film coating of HPMC on the drug pellets in the absence to drug pellets would have been greater. *In vitro* dissolution studies reveled that more that 80% loratidine was release within one hour from both the multiple unit tablet formulations results of dissolution studies for pseudoephedrine hydrochloride from pellets as well as its multiple unit tablets are depicted in the fig. 3

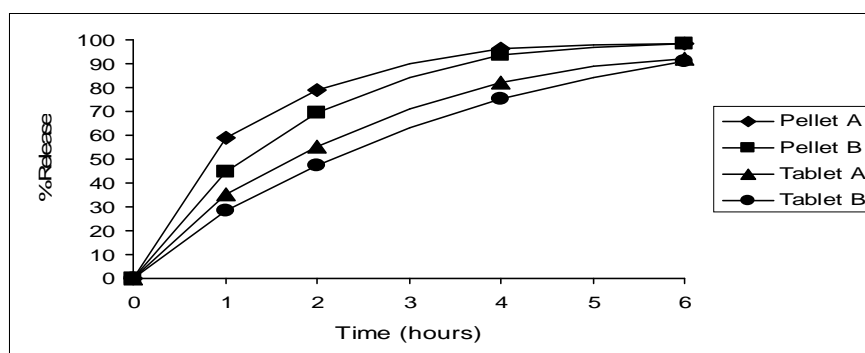


Figure 3. Dissolution profile of pseudoephedrine hydrochloride from film coated pellets (formulation A and B) and their respective multiple unit tablet formulation.

CONCLUSION

The resulting multiple-unit dosage forms designed for dual release profile were satisfactory. The compacts designed here were of acceptable mechanical strength. The tablets disintegrate rapidly *in vitro* to release virtually intact controlled-release pseudoephedrine pellets and loratidine. Cushioning excipients as well as the film coating on the pseudoephedrine pellets appeared to play key role in rapid disintegration of tablet and separation of discrete particles of both drugs. Photomicrographs showed that significant deformation of pellets exposed to the tablet punches and die had occurred during compression. In order to quantify in real terms the extent of this damage, the drug release profiles from uncompacted pellets and multiple-unit tablets were compared. The study showed that compaction further retarded the release of pseudoephedrine, which was owed to densification of pellets. However, the release of co-compressed loratidine was obtained as expected. The present study has thus demonstrated that hydrophilic gums that exhibit rapid swelling can be advantageously used to design controlled-release pellets, which retain their release characteristics even after compaction. Such formulations offer several benefits in comparison to multiple-unit tablets containing controlled-release pellets where release is primarily controlled by the polymeric membrane—ease, economy and rapidity of processing, flexibility in formulation design and maintenance of release characteristics after compaction. Such formulations are also advantageous as compared to conventional capsules containing controlled-release pellets in that size of dosage form is relatively small. The formulation designed here is also superior in comparison to controlled-release matrix tablets in that one can combine two or more drugs having different release characteristics in a single unit conveniently, and near zero-order release of the controlled-release component can still be retained.

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