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Novel Process Formulation of Multiple Unit Tablet of Pantoprazole

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Abstract**—**The present invention relates to multiple-unit tablet dosage forms, which is composed of several subunits (multiparticulates/pellets). Each small multiparticulate further composed of many layers. Some layer contains drug substance; others are rate controlling polymer. The resulting multiple-unit tablet dosage forms of pantoprazole were satisfactory fabricated. Pelletization technique has some advantages over coated tablet formulation. In coated tablet the coating may be damaged and a pinhole possibly formed that would result in increased release of drug in stomach and may be deactivated in stomach juices. If the coat of some pellets may be damaged that would not affect the release properties of the multiple-unit tablet. Hence they are beneficial in this aspect. The results confirmed the successful preparation of stable and bioequivalent once daily controlled release multiple-unit tablets of pantoprazole.

Keywords**—**Controlled release, multiple unit tablets, pantoprazole, pelletization.

I. Introduction

CONTROLLED release multiple-unit tablet or pellet formulations have gained immense popularity owing to their superiority over the conventional dosage form in several respects. Controlled absorption with reduction in peak to trough ratios, targeted release of the drug to specific areas within the gastrointestinal tract, absorption of drug irrespective of the feeding state, minimal potential for dose dumping and facility to produce combination of dosage forms [1].

Compaction of coated beads, pellets or spheroids into tablets combines the advantages of oral multiparticulates dosage forms with those of tablets, i.e. cost effectiveness and divisibility. One way to design oral controlled release system is to coat spherical granules (pellets/multiparticulates) with a polymer that regulates their drug release rate .Such reservoir pellets can be filled in hard gelatin capsules or compacted into multiple-unit tablets. These multiple-unit tablets are normally intended to disintegrate into discrete pellets in the gastrointestinal tract and the drug should subsequently be released in a controlled manner from the individual pellets. One challenge in the production of such multiple-unit pelletized tablets is maintaining the desired drug release after compaction as the application of compaction pressure can lead to structural changes of the film coating that consequently, may alter drug release.

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The compression induced changes in the structure of a film coating may depends upon formulation factors, such as type and amount of coating, thickness of coating ,structure of pellets and the incorporation of excipients at the time of compaction [2].

When a multiparticulate dosage product is developed in the form of a tablet, it is often enviable to produce compacts that disintegrate into many subunits soon after ingestion, to attain uniform concentrations of active substances in the body. It is imperative to emphasize the fact that the coated subunits in the formulations must withstand the process of compaction without being damaged. After compaction the existence of cracks has been reported in literature with a polymer (ethyl cellulose) coated on pellets. This may lead to undesirable effects on the drug release properties of those subunits. The type and amount of coating on pellets, the size of subunit, the surface properties of pellets, the selection of external and internal additives having a cushioning effect and the rate and magnitude of applied pressure must be carefully considered in the design of such a dosage form.

Pelletization technique has some advantages over coated tablet formulation. In coated tablet the coating may be damaged and a pinhole possibly formed that would result in increased release of drug in stomach and may be deactivated in stomach juices. Multiple-unit tablet formulation is composed of several subunits (multiparticulates/pellets). If the coat of some pellets may be damaged that would not affect the release properties of the multiple-unit tablet. Hence they are beneficial in this aspect.Spherical oral dosage forms such as pills have been used in the pharmaceutical industry for a long time, but the full impact of systematically agglomerated spherical units or pellets on controlled release oral dosage form design and performance was not realized till early 1970s [3]. These solid oral dosage form consists of a multiplicity of small discrete particulates i.e. pellet and granules. These systems provide flexibility during formulation development and therapeutic benefits to patients in last two decades. The prime significant advantage of multiparticulates is to attain desired doses without formulation or process changes. Furthermore, controlled-release multiple-unit dosage forms are less susceptible to dose dumping than the reservoir or matrix type single unit tablet since the drug release profile does not depend on the drug release properties of a single unit.Technological advances in dosage form design, the advent of highly specialized equipments and the popularity of controlled–release dosage forms as a means of drug delivery have made multiparticulate a viable and attractive alternative to single dosage forms [4].

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Multiparticulates (pellets) also have numerous therapeutic advantages over single unit dosage forms. When taken orally, multiparticulates generally disperse freely in the gastrointestinal tract, maximize absorption, minimize side effects, and reduce inter-and intrapatient variability.

II. Materials and Methods

A. Materials

Pantoprazole (Pantoprazole sodium sesquihydrate) was procured from Mcneil Pharma S.T.,Kangra,(H.P.) as gift sample. Non pareil seeds, PVPK-30, Purified talc, Eudragit L-100, Eudragit S-100, PEG-6000, Aerosil-200, MCC PH 101, lactose, Starch, Magnesium stearate, Methanol, Methylene chloride, Isopropyl alcohol and deionized water etc. were used in present research work.

All these excipients were of pharmacopoeial grade and were procured from Excellent pharma New-Delhi, Kanwarlal group of companies, Chennai, Sanmour pharma ltd., Mumbai, Jaipur pharmaceutical works, Jaipur (Rajasthan), Mcneil pharma S. T., Kangra, Himachal Pradesh and Sancure laboratory S.G.N.R, (Rajasthan).

III. Experimental

A. Preparation of Pantoprazole Pellets by Using Extrusion / Spheronization Techniques

Approximately 100 gm batch of pantoprazole and microcrystalline cellulose PH 101 in different concentrations were passed through sieve no.100 and then mixed in a mortar for 15 minutes. All the powders were blended by geometric dilution methods using pestle and mortar. Binder solution PVPK-30 (4 %) was added to powder blends. Purified water 50 ml was added to powder blends gradually and blend kneaded to get suitable wet mass. The moist wet mass was transferred into the extruder to obtain the extrudates. The extrudates were immediately transferred to a spheronizer. Wet pellets were dried in fluidized- bed dryer at 50^0 C for 12 hours.

TABLE I
Composition of Core Pantoprazole Pellets

S. No.	Batch	Pantoprazole (gm)	MCC PH 101 (gm)	PVPK-30 (gm)
1.	P-1	20	80	4
2.	P-2	25	75	4
3.	P-3	30	70	4
4.	P-4	40	60	4
5.	P-5	50	50	4
6.	P-6	60	40	4

B. Preparation of Pantoprazole Pellets Using Solution Layering Modified Roto Granulator Technique

The method utilized to produce pellets in a roto granulator involves surface layering of drug onto an inert substrate (non pareil seeds). Normally surface layering of a drug in a roto granulator is done on spherical shaped nonpareil seeds/ beads such as microcrystalline cellulose. Spherical shape of the pellets / starter seeds provides excellent rolling in the roto granulator and minimizes agglomerates and / or aggregation during processing. In addition, economic availability of such nonpareils has increased the popularity of processing pellets in a roto granulator, especially of low dose drug.

C. Processing of Pellets

The controlled release multiparticulates pellet formulation (PR-1) each containing 40 mg of pantoprazole in controlled release form were designed for once daily dosing. The formulations were, so designed that the preparations release not less than 80 % of drug in 18 hours. The drug dose (40 mg of pantoprazole) was contained in about 240-250 mg of final pellet formulation.

D. Pantoprazole Drug Loading on Nonpareil Seeds by Using Solution layering Roto Granulator Technology

Drug pellets of known amount batch size containing 40 mg of pantoprazole (pantoprazole sodium sesquihydrate) were prepared. PVPK-30 (25 gm) was weighed accurately and dissolved in purified water with constant stirring. The drug pantoprazole was dissolved in water with constant stirring and added to the above solution with constant slow stirring. Purified talc (shifted through 200 mesh sieves) was added to the above solution with constant stirring for fifteen minutes and the solution was filtered through 100 mesh sieves. The solutions were continuously sprayed on the starter seeds using a pneumatic pump and spray gun with a 1.0 mm nozzle at the rate enough to prevent over wetting and agglomeration of pellets. After the completion of the process, the pellets were rolled for additional 30 minutes, before subjecting to tray drying. After the completion of drug loading process, the drug pellets were dried in a tray dryer at 55-60^0C temperature for 20-24 hours. The dried pellets were shifted to collect 12-20 mesh fraction, 12 mesh over size (agglomerates) and 20 mesh undersize (Fines).

TABLE II
Composition of Pantoprazole Drug Pellets

S. No.	Ingredients	Qty (mg)/ tablet	Qty (gm)/ batch
1.	N.P.seed (800-1000 µ)	80.9	202.25
2.	Pantoprazole 40 mg equivalent to pantoprazole sodium sesquihydrate 45.10 mg	45.10	112.75
3.	PVPK-30	10.0	25
4.	Purified talc	15.0	37.5
5.	Purified water (RC 20 %)	0.38	950

E. Coating Process

1. Seal Coating on Pantoprazole Pellets

Approximately 500 gm pellets of optimized batch's P-1 and PR-1 were divided into two parts of 250 gm each and transferred into a roto granulator (fluidized-bottom side spray system) and then coated with seal coating solution HPMC E-15 and HPMC E-5 respectively. Formula for seal coating details is indicated as below. During the coating operations the coating solution was continuously stirred in order to prevent sedimentation of the insoluble materials.

The operation conditions during the coating process were as follows: inlet and outlet temperatures of drying air were 55-

60^0C and 35-40^0C respectively. Pneumatic spraying pressure and spraying rate were set correspondingly at 1.5 bars and 7.5 gm/min. After coating, the resulted coated pellets were dried at 50-60 ^{0}C for 24 hours. The processing conditions employed for seal coating on pantoprazole drug pellets are depicted as following.

2.Coating Formula for Controlled Release

Controlled / Enteric coated dosage forms are designed to resist irritation in stomach and destructive action by gastric fluids. Solution of acrylic polymers in organic solvents were utilizes as the controlled release / enteric coating in the present research formulation. Eudragit L-100 and eudragit S-100 were used to coat pantoprazole pellets. The polymeric coating of pellets must remain intact during compression in order to retain its controlled release properties [4].

TABLE III
FORMULA FOR SEAL COATING

S. No	Ingredients	P-7	P-8	PR-2	PR-3
1.	HPMC E-15 (gm)	25		50	
2.	HPMC E-5 (gm)		25		50
3.	Poly ethylene glycol -6000(gm)	10	10	10	10
4.	Purified talc (gm)	10	10	10	10
5.	Iso propyl alcohol (gm)	750	750	750	750
6.	Methylene chloride (gm)	750	750	750	750

TABLE IV
PROCESS CONSTRAINT OF ROTO GRANULATOR DURING SEAL COATING ON PANTOPRAZOLE PELLETS

S. No.	Parameters	P-7	P-8	PR-2	PR-3
1.	Inlet air temperature (^{o}C)	58	55	55-60	55-60
2.	Process bed temperature (^{o}C)	38	36	35-40	35-40
3.	Exhaust air temperature (^{o}C)	42	42	45	45
4.	Atomization pressure (bar)	1.5	1.5	1.5	1.5
5.	Pneumatic pump speed (rpm)	08	08	08	08
6.	Spray rate (gm/min.)	7.5	7.5	7.5	7.5
7.	Disc frequency	8.1	8.1	8.1	8.1
8.	Damper Inlet (%)	65	65	65	65
9.	Exhaust /Outlet (%)	80	80	80	80
10.	Room humidity (%)	65-70	65-70	65-70	65-70
11.	Processing time (hrs)	2	2.1	2.5	2.5

F. Preparation of Eudragit L-100 and Eudragit S-100 Dispersion

The weighed quantities of eudragit L-100 and eudragit S-100 were dissolved in mixture of IPA and methylene chloride. Poly ethylene glycol-6000 were dissolved in mixture of IPA and methylene chloride and transferred to eudragit L-100 and eudragit S-100 solution separately under slowly stirring conditions. Purified talc was dispersed in the above solution and stirred continued for about 30 minutes until uniform solution is obtained**.**

G. Controlled Release Coating Process

The seal coating pellets of different batches P-7, P-8, PR-2 and PR-3 were transferred into a roto granulator and coated with different controlled release coating solution [5]. The formula was shown as below. During the coating operations; the coating solution was continuously stirred in order to prevent sedimentation of the insoluble material. The operating conditions during the coating process were as follows: inlet and outlet temperatures of drying air were 56-58 ^{0}C and 30-32 ^{0}C respectively [6]. Pneumatic spraying pressure and spraying rate were set correspondingly at 1.5 bars and 7.5 gm/min. After coating, the resulted coated pellets were dried at 60-65 ^{0}C for 24 hours. Process constraint of roto granulator during controlled release [7] coating on pantoprazole drug and seal loaded pellets are shown in Table V.

TABLE V
FORMULA OF CONTROLLED RELEASE COATING MATERIALS

S. No.	Ingredients(gm)	P-7	P-8	PR-2	PR-3
1.	Eudragit L-100	50	-	20	-
2.	Eudragit S-100	-	50	-	20
3.	Poly ethylene glycol -6000	20	20	20	20
4.	Purified talc (gm)	20	20	20	20
5.	Iso Propyl Alcohol (gm)	1500	1500	1500	1500
6.	Methylene chloride (gm)	1500	1500	1500	1500

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TABLE VI
PROCESS CONSTRAINT OF ROTO GRANULATOR DURING CONTROLLED RELEASE COATING ON PANTOPRAZOLE DRUG AND SEAL LOADED PELLETS

S. No.	Parameters	P-7	P-8	PR-2	PR-3
1.	Inlet air temperature (^{o} C)	56-58	56-58	56-58	56-58
2.	Process bed temperature (^{o} C)	30-32	30-32	30-32	30-32
3.	Exhaust air temperature (^{o} C)	40-42	40-42	40-42	40-42
4.	Atomization pressure (bar)	1.5	1.5	1.5	1.5
5.	Pneumatic pump speed (rpm)	08	08	08	08
6.	Spray rate (gm/min.)	7.5	7.5	7.5	7.5
7.	Disc frequency	8.1	8.1	8.1	8.1
8.	Damper Inlet (%)	65	65	65	65
9.	Exhaust /Outlet (%)	70	70	70	70
10.	Room humidity (%)	60-70	60-70	60-70	60-70
11.	Processing time (hrs)	2.5	2.5	2.5	2.5

H. Compaction of Pantoprazole Controlled Release Pellets into Tablets

Depending upon the additives used to provide cushioning effects, six multiple-unit tablet formulations of each method were premeditated. All the six formulations are contained pantoprazole pellets in seal and controlled release form [8].

I. Procedure

Drug pellet of known amount of approximately 286 gm of batches P-19 and 281 mg of batches PR-2 contains 40 mg of pantoprazole equivalent to pantoprazole sodium sesquihydrate 45.10 mg were obtained after seal and controlled release coating. Direct compression technique was adopted for preparing the pantoprazole controlled release multiple unit-tablets. Batch size of the each formulation was 500 tablets. The formula is shown following table. Each batch was divided into three parts. The procedure involved-

1. Sifting the directly compressible excipients i.e. spray-dried microcrystalline cellulose and spray dried lactose through 40 mesh size sieve.
2. The formulation P-9 and PR-5 contained pantoprazole controlled release pellets, spray dried microcrystalline cellulose PH 101 and spray dried lactose in quantities of 10 mg, 20 mg and 50 mg each as the cushioning agents.
3. The formulation P-10 and PR-6 contained pantoprazole controlled release pellets, MCC and non pareil seeds (composed of MCC) as the cushioning beads in quantities of 10 mg and 20 mg and 50 mg each as the cushioning beads**.**
4. The formulation P-11 and PR-4 contained pantoprazole controlled release pellets and spray-dried microcrystalline cellulose as cushioning excipients. These cushioning excipients required to fill efficiently the void space between the pellets. The quantity of MCC used in this formulation is 30 mg and 100 mg in each tablet for the present study, while designing the tablet formulation.
5. Blending the mixture of step-2, 3 and 4 with starch, purified talc, magnesium stearate and aerosil respectively.
6. Compaction the blends of step no-5 into multiple-unit tablet using cadmach eight station tablet compression machine.
7. The compaction force applied for compaction is 5 kN.
8. Drying the tablets in a tray dryer at 45- 50 ^{0}C for 12 hours.
9. Film coating of tablets in rota granulator with HPMC as the coating polymer, as the same conditions described in coating of pantoprazole drug pellets. Film coating of multiple-unit tablets in rota granulator was made with HPMC as the coating polymer. HPMC was first dissolved in purified water under stirred condition. Polyethylene glycol-6000 was dissolved in slightly hot water and then incorporated in the polymer solution with slowly stirring. Purified talc was firstly sifted through 200 mesh screen and then incorporated into the solution of polymer under slowly stirred conditions. The polymeric solution was further stirred for 20 minutes to obtained smooth and homogenous coating solution [9]. This coating solution was passed through 100 mesh nylon cloth. The processing conditions employed for coating of multiple-unit pantoprazole tablet formulations are depicted in following table.

J. Evaluation of Multiple-Unit Tablet of Pantoprazole

The pantoprazole compressed tablets prepared by extrusion /spheronizer technology and solution layering technology were evaluated for following parameters [10].

1. Tablet hardness
2. Friability
3. Uniformity of weight
4. Disintegration test
5. *In vitro* dissolution studies

IV. RESULTS AND DISCUSSION

A. Evaluation of Multiple-Unit Pantoprazole Tablet

Table VII shows the results of multiple-unit tablets of pantoprazole .The possibility of preparing multiple-unit tablets containing a controlled release drug was practically evaluated in the present research work. Satisfactory tablets having good mechanical strength were produced with formulations P-23 and PR-4.The good mechanical strength as evaluated on the basis on hardness and friability values. The formulations P-21, P-22, PR-5 and PR-6 showed not good mechanical strength. Some cracks were also pragmatic on the surface of tablets. Disintegration of all the formulations was fast, thereby releasing pantoprazole pellets in the dissolution fluids. All formulations complied for weight variation test. Friability results indicated that the percentage loss was not more than 1

Open Science Index, Pharmacological and Pharmaceutical Sciences Vol:7, No:9, 2013 publications.waset.org/16694/pdf

%. The pantoprazole pellets release the drug in a controlled release manner autonomously, a characteristic predictable from such multiple-unit tablet systems. Formulations P-23 and PR-4 passed the uniformity of weight test.

TABLE VII
RESULTS OF COMPACTED MULTIPLE UNIT TABLETS OF PANTOPRAZOLE

Parameters	P-21	P-22	P-23	PR-4	PR-5	PR-6
Hardness	6.5 kg/cm^3	8.2 kg/cm^3	8.0 kg/cm^3	8.1 kg/cm^3	9.0 kg/cm^3	8.5 kg/cm^3
Friability	0.7%	0.7%	0.8%	0.7 %	0.5%	0.9%
Disintegration time	10 min.	11 min.	8 min.	5 min.	5 min.	5 min.
Uniformity of weight	0.3299 ± 0.0085	0.3234 ± 0.0025	0.3398 ± 0.0065	0.4264 ± 0.0106	0.4197 ± 0.0200	0.4230 ± 0.0015

B. In Vitro Release Profile of Multiple-Unit Tablet Formulations of Pantoprazole

The results of dissolution study are shown in Table VIII and in Fig. 1. All the six tablet formulations after compaction showed an initial burst effect and later on diffusion effects, which is characteristic of such systems, followed by completely unswerving drug release pattern. Tablet formulation P-21 after compaction showed 5.94 % of release of pantoprazole drug after 2 hours, 87.83 % of drug release within 18 hours and 99.08 % drug released between 22-24 hours. This also shows the change release pattern as shown by the previously formed pellets formulation P-19.This also lost their little controlled release properties after compression into tablets.

Formulation P-22 after compaction showed 5.80% releases of pantoprazole drug within 2 hours, 80.25 % of drug release within 18 hours and 95.42% drug release between 24 hours. This shows the change release pattern as shown by the previously formed pellets formulation of batch P-19. This is due to damage of coating after compaction of pellets. Formulation P-23 after compaction showed 9.91% release of pantoprazole drug within 2 hours, 83.31 % of drug release within 18 hours and 98.34% drug release between 24 hours. This shows no change in release pattern as shown by the pellet formulation P-19. Formulation PR-4 tablet showed 5.03% within 2 hours and 82.22 % of pantoprazole release within 18 hours and 95.23 % of drug release between 24 hours. The formulation showed no change in release profile as compared to pellet formulation PR-2. Formulation PR-5 tablet showed 7.55 % within 2 hours and 88.00 % of pantoprazole release within 18 hours and 98.00 % of drug release between 24 hours. There was increase in release rate as compared to pellet formulation of batch PR-2, because of breaking of coating after compaction. Formulation PR-6 tablet showed 5.55 % of drug release within 2 hours,79.39% of pantoprazole release within 18 hours and 99.23% drug release between 24 hours. This shows change in release profile after pellets compaction. The difference in the initial burst effect between the three formulations are largely attributes to design the system and also to the film coating. Maximum burst effect was found in formulation P-21, P-22, PR-5 and PR-6 and minimum effect was found in formulation P-23 and PR-4. The formulation P-22 and PR-6 also have shown that reservoir pellets (Non pareil seeds) can undergo extensive structural changes, in terms of deformation and densification during compaction, with a diminutive drug release time. The formulation under study concluded that controlled release tablet of formulations P-23 and PR-4 of pantoprazole showed significant drug release profile unto 24 hours. Thus the dissolution study showed that multiple-unit tablets of pantoprazole were a successful tablet formulation as controlled release purposes and also indicating that the both preparations are suitable for once daily dosing.

TABLE VIII
IN VITRO RELEASE PROFILE OF MULTIPLE UNIT TABLETS OF PANTOPRAZOLE FORMULATION

S. No.	**Time**	**Medium**	**Cumulative release (%)**					
	(hrs)	**(pH)**	**P-21**	**P-22**	**P-23**	**PR-4**	**PR-5**	**PR-6**
1	0	0	0	0	0	0	0	0
2	1	1.2	3.56	2.23	4.35	3.32	4.1	3.34
3	2	1.2	5.94	5.80	9.91	5.03	7.55	5.55
4	4	6.8	15.00	14.26	20.79	13.05	14.58	10.54
5	6	6.8	27.65	25.40	35.87	23.35	28.04	26.06
6	8	6.8	39.81	36.59	42.07	31.49	37.60	31.46
7	10	6.8	52.96	45.77	54.27	45.53	45.50	47.04
8	12	6.8	63.86	54.70	67.21	59.01	58.83	51.88
9	14	6.8	79.238	65.29	75.99	71.84	69.96	62.68
10	16	6.8	86.26	73.80	80.69	78.63	82.21	71.27
11	18	6.8	87.83	80.25	83.31	82.22	88.00	79.39
12	20	6.8	92.06	88.09	85.67	85.12	95.34	83.09
13	22	6.8	98.06	90.45	90.45	91.34	97.23	89.00
14	24	6.8	99.08	95.42	98.34	95.23	98.00	99.23

V. CONCLUSION

The main objective of this present research work was development of an oral multiple-unit pantoprazole tablet formulation. The intention was to prepare a formulation using HPMC seal coating, Eudragit L-100 as acrylic polymers and microcrystalline cellulose as cushioning excipient, that

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compacts the pantoprazole pellets without deforming and release the drug up to 22-24 hours.

The formulations developed also have to prevent drug liberation from the stomach. The resulting multiple-unit tablet dosage forms designed for controlled and enteric release profile were satisfactory fabricated. The compacts designed by different methods were of acceptable mechanical strength. The tablets disintegrate rapidly in vitro to give controlled release pantoprazole pellets. Microcrystalline cellulose as cushioning excipients, hydroxy propyl methyl cellulose and acrylic polymers coating on pantoprazole pellets play a vital role in rapid disintegration of multiple-unit tablet and separation of discrete particles (pellets) of both methods prepared pelletized tablets. Scanning electron microscopy showed that there is no deformation of pellets exposed to the tablet punches and die at the time of compaction.

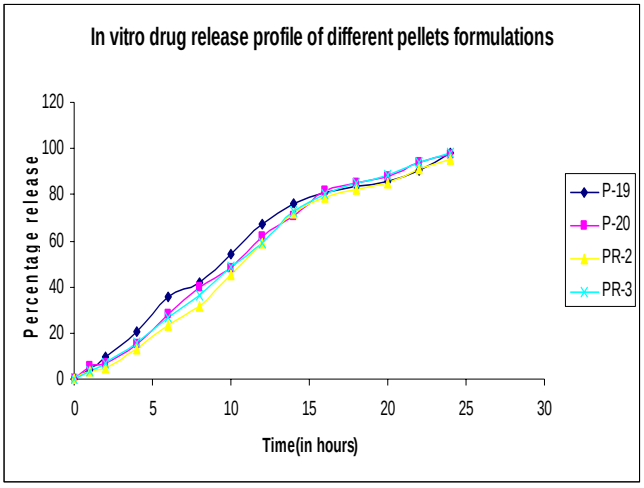


Fig. 1 *In vitro* release profile of multiple unit tablets of pantoprazole formulation

In order to reckon in existent terms the amount of damage to controlled release pellets due to compaction, drug release profiles from un compacted pellets and multiple-unit tablets were compared. The present compaction study further concluded that there were no changes in drug release profile observed after compaction and when microcrystalline cellulose was used as excipients.

The present research work has thus demonstrated that the use of hydroxy propyl methyl cellulose seal coating and acrylic polymers as controlled release coating that exhibits the stress at the time of compaction. This also retains their controlled release characteristics even after compaction. The formulation designed here is also superior in comparison to controlled release matrix tablets for the simple reason that near to zero-order release or first order release of drug is possible. The formulation developed was screened for pharmacological activity and results suggested it as a safe and effective formulation. Amongst the six tablet formulations designed, the ease of formulation lies with fabrication of formulation P-23 and PR-4, since it requires lesser number of processing steps to achieve the same controlled release characteristics. Such multiple- unit formulations also advantageous as compared to conventional capsules containing controlled release pellets in that the size of dosage form is relatively small and that the cost of formulation is low since there is no need to use the capsule shell. The present study confirmed that controlled release multiparticulate tablet systems could be successfully designed using HPMC-15 and acrylic polymer (Eudragit L-100).

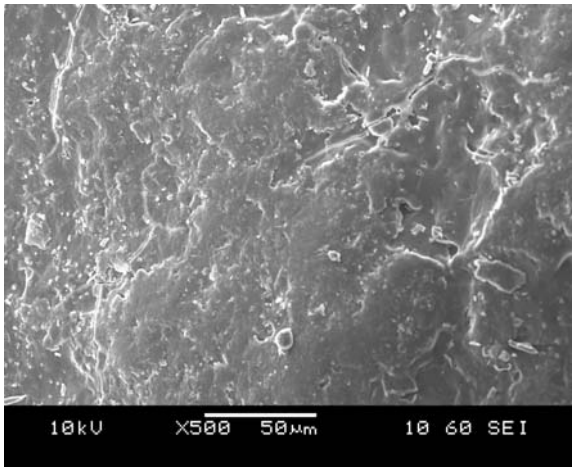


Fig. 2 SEM photographs of surfaces of pantoprazole pellets of batch PR-4 after compaction

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